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Improving and Expanding Estimates of the Global Burden of Disease Due to Environmental Health Risk Factors

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Background: The Global Burden of Disease (GBD) study, coordinated by the Institute for Health Metrics and Evaluation (IHME), produces influential, data-driven estimates of the burden of disease and premature death due to major risk factors. Expanded quantification of disease due to environmental health (EH) risk factors, including climate change, will enhance accuracy of GBD estimates, which will contribute to developing cost-effective policies that promote prevention and achieving Sustainable Development Goals.

Objectives: We review key aspects of the GBD for the EH community and introduce the Global Burden of Disease–Pollution and Health Initiative (GBD-PHI), which aims to work with IHME and the GBD study to improve estimates of disease burden attributable to EH risk factors and to develop an innovative approach to estimating climate-related disease burden—both current and projected.

Methods: We discuss strategies for improving GBD quantification of specific EH risk factors, including air pollution, lead, and climate change. We highlight key methodological challenges, including new EH risk factors, notably evidence rating and global exposure assessment.

Discussion: A number of issues present challenges to the scope and accuracy of current GBD estimates for EH risk factors. For air pollution, minimal data exist on the exposure–risk relationships associated with high levels of pollution; epidemiological studies in high pollution regions should be a research priority. For lead, the GBD's current methods do not fully account for lead's impact on neurodevelopment; innovative methods to account for subclinical effects are needed. Decisions on inclusion of additional EH risk–outcome pairs need to be guided by findings of systematic reviews, the size of exposed populations, feasibility of global exposure estimates, and predicted trends in exposures and diseases. Neurotoxicants, endocrine-disrupting chemicals, and climate-related factors should be high priorities for incorporation into upcoming iterations of the GBD study. Enhancing the scope and methods will improve the GBD's estimates and better guide prevention policy. https://doi.org/10.1289/EHP5496

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Introduction

The Global Burden of Disease Study (GBD), coordinated by the Institute for Health Metrics and Evaluation (IHME), has emerged as the largest systematic, data-driven effort to quantify the magnitude of health loss from all major diseases and injuries. GBD estimates have influenced global public health research, policy, education, and action on a wide range of diseases and risk factors. Examples of these data-driven impacts are the initiation of free short-term depression therapy in Australia, restructuring of health insurance coverage to align with major causes of disease in Mexico, and construction of new roads and retraining of police to address the high burden of traffic injuries in Iran (Smith 2015).

IHME's comparative risk assessments have focused attention on the magnitude of the global burden of disease caused by air pollution since 2010, alongside other major health risk factors such as smoking, diet, and obesity (WHO 2019). These estimates placed reduction of exposure to ambient and household air pollution squarely on the global health agenda, eliciting high-level government responses in China and India, and provide key metrics for several Sustainable Development Goals (SDGs). In its 2017 publication, the *Lancet* Commission on Pollution and Health used 2015 GBD data to calculate that the combined pollution of air, water, and soil by chemicals was responsible for 268 million disability-adjusted life-years (DALYs) and 9 million premature deaths each year—more than 3 times the total annual deaths caused by HIV/AIDS, tuberculosis, and malaria—with the greatest burden in low- and middle-income countries (LMICs) (Landrigan et al. 2018a). The 2017 GBD study estimated that specific environmental health (EH) risk factors accounted for 8.32 million deaths and 308 million DALYs (Stanaway et al. 2018). Meanwhile, the World Health Organization (WHO), which had been making its own estimates of the global burden of disease parallel to IHME, produced data for environmental impacts in 2017 that were in a similar range (Prüss-Ustün et al. 2017); shortly thereafter, WHO and IHME signed an agreement to collaborate, jointly making all GBD estimates going forward.

Although large, these estimates capture only a fraction of the burden associated with the limited EH risk factors included in the GBD analysis: certain air pollutants, water, lead, and occupational exposures. In response, the Global Burden of Disease–Pollution and Health Initiative (GBD-PHI) was formed. This new initiative aims to work with the GBD to improve and expand estimates of the global burden of disease attributable to an expanded set of EH risk factors, including current and projected climate-related disease burden. Here, we provide an overview of the GBD to the EH community and then articulate some of the ideas, challenges, and opportunities associated with the GBD-PHI, which were discussed at an inaugural workshop in March 2018 (Hu et al. 2018) and have been the subject of ongoing discussions. We outline an ambitious research agenda for the GBD-PHI, first by providing an overview of GBD methods for estimating exposure to risk factors and the associated burden, followed by a focus on air pollution and lead as two case studies. We then discuss the challenges and opportunities associated with grading the evidence for causality and combining these considerations to rank and prioritize EH risk factors for inclusion in the GBD. Finally, we discuss neurotoxicants and endocrine disrupting chemicals (EDCs) as examples of likely high-priority classes of candidates for inclusion in the GBD, and we consider the special challenges of estimating the burden of disease and death related to climate change. A summary of the proposed research agenda and recommendations is provided in Appendix 1.

As stated in the GBD Protocol, "an uncertain estimate … is preferable to no estimate because no estimate is often taken to mean no health loss from that condition" (IHME 2018). Ultimately, by more fully documenting the current and anticipated impacts and risks of EH exposures on the burden of disease and death at the subnational, national, and international scales, countries will be better able to prioritize pollution control investments that promote long-term stability, growth, and prosperity.

GBD Overview and Existing EH Risk Factors

A full description of the GBD, GBD methods, and the most recent assessment of risk factors and associated burden for 195 countries and territories can be found in recent publications and associated appendices (James et al. 2018; Kyu et al. 2018; GBD 2017; Roth et al. 2018; Stanaway et al. 2018). Briefly, the GBD is coordinated by the IHME with the assistance of a network of more than 3,600 researchers in more than 145 countries. Using a comparative risk assessment approach, it organizes behavioral, environmental, occupational, and metabolic risk factors into five hierarchical levels. Level 0 includes the aggregated estimates for all risk factors combined. Level 1 includes three risk groups: *a*) environmental and occupational risks, *b*) metabolic risks, and *c*) behavioral risks. Each subsequent level includes more-detailed risk factors that are nested within the broader category above it (Figure 1).

Each risk factor is associated with one or more outcomes, and each combination of risk factor and outcome is referred to as a risk–outcome pair. Risk–outcome pairs are assessed for inclusion based primarily on two factors: *a*) the strength of evidence for a causal association between the risk and outcome, and, *b*) the feasibility of developing the necessary globally complete estimates of exposure levels. The process for assessing causal evidence focuses on identifying, screening, rating, and analyzing epidemiological studies, concluding with a weight of evidence determination following the World Cancer Research Fund criteria (World Cancer Research Fund/American Institute for Cancer Research 2018); the feasibility of estimating exposures is assessed based on available data, predictive covariates, and analytical methods. Risk–outcome pairs that are judged to meet the above criteria are presented for final review for approval by the GBD Scientific Council composed of subject-matter experts (IHME).

To calculate the attributable burden for each risk–outcome pair, the GBD requires for all locations: *a*) a burden estimate for the outcome [e.g., number of deaths, years of life lost (YLL), and DALYs]; *b*) spatially and temporally resolved exposure estimates for the risk factor; *c*) the counterfactual or theoretical minimum risk exposure level (TMREL); and *d*) the relative risk (i.e., exposure–response relationship) for the outcome, relative to the TMREL. The population attributable fraction (PAF) is defined as the proportion of the outcome, for a given population and year, that would be eliminated if the risk factor were reduced to the TMREL, and it is calculated from the last three of the aforementioned inputs. Risk-attributable disease burden is estimated for each risk–outcome pair by age group, sex, and location. GBD locations are arranged in a hierarchy: in GBD 2017, 195 countries and territories are nested within 21 regions, which in turn, are within 7 super-regions. Subnational estimates are made for countries with populations larger than 200 million as well as a select set of other countries.

To calculate years lived with disability (YLDs), GBD employs disability weights to quantify the severity of the health loss associated with different health states. Beginning in GBD 2010, the assignment of disability weights has involved an iterative ranking process whereby members of the general public are given descriptions of sequelae from two health states using nonclinical terminology and asked to rate which set of sequelae connotes a healthier individual. Results are analyzed to assess agreement between

Level 0	Level 1	Level 2	Level 3	Level 4
All risk factors	Environmental/ occupational risks	Unsafe water, sanitation, and handwashing	Unsafe water source	
			Unsafe sanitation	
			No handwashing with soap	
		Air pollution	Particulate matter pollution	Ambient particulate matter pollution
				Household air pollution from solid fuels
			Ambient ozone pollution	
		Other environmental risks	Residential radon	
			Lead exposure	
		Occupational risks	Occupational carcinogens	
			Occupational asthmagens	
			Occupational particulate matter, gases, and fumes	
			Occupational noise	
			Occupational injuries	
			Occupational ergonomic factors	
	Behavioral risks	Child and maternal malnutrition	Suboptimal breastfeeding	Non-exclusive breastfeeding
				Discontinued breastfeeding
			Childhood undernutrition	Childhood underweight
				Childhood wasting
				Childhood stunting
			Iron deficiency	
			Vitamin A deficiency	
			Zinc deficiency	
		Tobacco smoke	Smoking	
			Second-hand smoke	
		Alcohol use		
		Drug use		
		Dietary risks		
		Intimate partner violence		
		Childhood maltreatment	Childhood sexual abuse	
			Bulllying victimization	
		Unsafe sex		
		Low physical activity		
	Metabolic risks	High fasting plasma glucose		
		High LDL cholesterol		
		High systolic blood pressure		
		High body-mass index		
		Low bone mineral density		
		Low glomerular filtration rate		

Figure 1. Global Burden of Disease Study (GBD) risk factor hierarchy (adapted from Stanaway et al. 2018).

participants on pairings and then weights are generated on a scale from 0 to 1, where 0 indicates no health loss, and 1 indicates total health loss (i.e., equivalent to death) (Haagsma et al. 2015; Salomon et al. 2015). In GBD 2017, disability weights were estimated for 234 unique health states (Stanaway et al. 2018).

The GBD uses a number of approaches to deal with complex statistical challenges, such as the incorporation of data that are uneven in uncertainty and distribution within time intervals, vary across time intervals, are prone to gaps in the data sequence over time, or that follow nonlinear trends. Specific examples and detailed explanations are provided in the appendices of the most recent publication (Stanaway et al. 2018).

In the most recent iteration, 84 behavioral, environmental/occupational, and metabolic risks or risk groups were evaluated, and burden was estimated for 476 risk–outcome pairs. The specific EH risk factors included in this assessment were unsafe water, sanitation, and handwashing; air pollution [ambient ozone and fine particulate matter ($PM_{2.5}$), and household $PM_{2.5}$]; residential radon; lead; and occupational exposures to carcinogens (asbestos, arsenic, benzene, beryllium, cadmium, chromium, diesel exhaust, formaldehyde, nickel, polycyclic aromatic hydrocarbons, silica, sulphuric acid, trichloroethylene), as well as occupational asthmagens, particulate matter (PM)/gases, noise, injuries, and ergonomic factors. These EH risk factors were estimated to contribute to 8.32

Table 1. Summary of epidemiological evidence used to determine risk–outcome relationships for unsafe water, air pollution, radon, and lead in the Global Burden of Disease Study (GBD) 2017 (adapted from Stanaway et al. 2018).

Risk factor	Outcome	Study type		
		RCTs (*n*)	Prospective observational studies (*n*)	Case–control studies (*n*)
Unsafe water, sanitation, and handwashing				
Unsafe water source – chlorination or solar (point of use treatment)	Diarrheal diseases	25	6	
Unsafe water source – piped	Diarrheal diseases	1	9	
Unsafe water source – filter	Diarrheal diseases	11	2	
Unsafe water source – improved water	Diarrheal diseases	0	5	
Unsafe sanitation – piped	Diarrheal diseases	0	7	
Unsafe sanitation – improved sanitation	Diarrheal diseases	1	11	
No access to handwashing facility	Diarrheal diseases	19	0	
No access to handwashing facility	Lower respiratory infections	8	11	
Air pollution: Particulate matter pollution				
Ambient particulate matter pollution	Lower respiratory infections	0	17	
Ambient particulate matter pollution	Tracheal, bronchus, and lung cancer	0	30	
Ambient particulate matter pollution	Ischemic heart disease	0	16	
Ambient particulate matter pollution	Ischemic stroke	0	30	
Ambient particulate matter pollution	Intracerebral hemorrhage	0	30	
Ambient particulate matter pollution	Subarachnoid hemorrhage	0	30	
Ambient particulate matter pollution	Chronic obstructive pulmonary disease	0	12	
Ambient particulate matter pollution	Diabetes mellitus type 2	0	8	
Household air pollution from solid fuels	Lower respiratory infections	2	8	17
Household air pollution from solid fuels	Tracheal, bronchus, and lung cancer	0	0	28
Household air pollution from solid fuels	Ischemic heart disease	0	2	2
Household air pollution from solid fuels	Ischemic stroke	0	1	
Household air pollution from solid fuels	Intracerebral hemorrhage	0	1	
Household air pollution from solid fuels	Subarachnoid hemorrhage	0	1	
Household air pollution from solid fuels	Chronic obstructive pulmonary disease	0	0	11
Household air pollution from solid fuels	Diabetes mellitus type 2	0	1	
Household air pollution from solid fuels	Cataract	0	0	8
Ambient ozone pollution	Chronic obstructive pulmonary disease	0	3	
Other environmental risks				
Residential radon	Tracheal, bronchus, and lung cancer	0	1	29
Lead exposure	Idiopathic developmental intellectual disability	0	8	
Lead exposure	Systolic blood pressure	0	3	1

Note: See original table for primary references. (Adapted from Appendix 1, Table 1 Stanaway et al. 2018).

million deaths and 308 million DALYs in 2017, in comparison with 8.15 million deaths and 345 million DALYs in 2007 (Stanaway et al. 2018). Given that most EH risk–outcome pairs cannot be assessed by randomized controlled trials (RCTs), the hierarchy of evidence involves assessing and weighing the results of prospective observational cohort and case–control studies that meet quality control standards (Table 1).

Discussion

In the following discussion, we have deliberately chosen to focus on environmental pollutants to which the general population is exposed, using air pollution and lead as case studies of EH risk factors currently incorporated in the GBD, as well as climate change. In so doing, we acknowledge that the communicable diseases associated with sanitation, hygiene, and unsafe water account for a large proportion of the GBD associated with the environment and remain a major global environmental health challenge for much of the world. Similarly, we acknowledge that occupational hazards exist throughout the world. However, we argue that these risk factors are relatively well-established and recognized, whereas, by comparison, environmental pollutants and their impacts on populations remain relatively under-recognized, with the vast majority entirely unaccounted for.

Case Studies of Current EH Risk Factors in the GBD

Air pollution. The GBD has included estimates of disease and premature death due to air pollution since 1990; major urban areas were included in GBD 2000 and extended to the global population in GBD 2010 (Lim et al. 2012; Murray et al. 2012), when the current methods for estimating exposure and risk were introduced. These innovations produced estimates of burden that ranked air pollution exposure as one of the leading risk factors for premature mortality globally. With each update, the GBD incorporates new exposure and epidemiological data and methods to improve the quality and scope of its estimates. The GBD's partnership with the Health Effects Institute (HEI), among other collaborators, has been instrumental in this work.

The GBD currently estimates the burden attributable to air pollution exposure for three categories: ambient $PM_{2.5}$, ambient ozone, and $PM_{2.5}$ from household use of solid fuels for cooking (Chen et al. 2008; Hoek et al. 2013). These three risk factors are globally measurable exposures that represent largely (though not entirely) independent sources contributing to the disease burden attributable to air pollution. Ambient $PM_{2.5}$ is the most robust predictor of mortality in studies of long-term exposure to air pollution. Ozone, a gas produced in photochemical atmospheric reactions of precursor emissions, is independently (from $PM_{2.5}$) associated with respiratory disease (Malley et al. 2017; Turner et al. 2016). Household air pollution from the use of solid fuels for cooking, although contributing to ambient $PM_{2.5}$, is itself a disease risk factor, independent of the surrounding outdoor pollution levels (Bruce et al. 2015; Fatmi and Coggon 2016; Gordon et al. 2014). Details on exposure estimation have been published previously (Cohen et al. 2017; Shaddick et al. 2018a; Stanaway et al. 2018). Briefly, population-weighted annual average exposure to ambient $PM_{2.5}$ is informed by chemical transport models and remote sensing estimates produced at 11 kilometer (km) $\times$ 11 km spatial resolution

with calibration to ground-level measurements (including the WHO Global Urban Ambient Air Pollution Database) (Shaddick et al. 2018a; Shaddick et al. 2018b; Stanaway et al. 2018; Van Donkelaar et al. 2016). Ozone exposure is based on a fusion of multiple chemical transport model estimates and available ground monitoring data to estimate the maximum seasonal (6-month) mean of daily 8 h maximum concentrations for each grid cell (Chang et al. 2019). Household $PM_{2.5}$ exposure is estimated from survey data about solid cooking fuel use and measurements of $PM_{2.5}$ concentrations in households using solid fuels for cooking (IHME and World Bank Group 2016). Recent revisions to the GBD methods have reduced the potential for double-counting of disease burden from household and ambient air pollution in locations where both risks are present. The combined burden from the two risk factors is first estimated and then split in proportion to their contributions to exposure levels. This revision led to decreases in the burden attributable to both of these risk factors. Other air pollutants, such as nitrogen dioxide (NO_2), may be included in future cycles of the GBD as global exposure estimates become available (Larkin et al. 2017) and evidence on their role as independent risk factors accumulates. For example, a recent estimate suggests that nearly 15% of global pediatric asthma incidence was attributable to NO_2 (Achakulwisut et al. 2019).

Exposure estimates for a given population are then combined with cause-specific exposure–response functions to calculate the corresponding PAF (Stanaway et al. 2018). The exposure–response functions for ambient and household $PM_{2.5}$ are derived from relative risk (RR) estimates for mortality from ischemic heart disease (IHD), stroke, lung cancer, chronic obstructive pulmonary disease (COPD), lower respiratory infections (LRI), and Type II diabetes from published cohort and case–control studies. Nonlinear functions were fit to RR estimates from studies of exposure to ambient PM, household air pollution, secondhand smoke, and active smoking to characterize exposure–response functions for exposure to $PM_{2.5}$ across the globally observed range [the Integrated Exposure–Response function (IER)] (Burnett et al. 2014; Cohen et al. 2017). The most recent estimate based on the IER was that 4.6 (UI 4.1–5.0) million deaths were attributable to ambient and household $PM_{2.5}$ in 2017 (Stanaway et al. 2018). A novel risk function based only on epidemiological studies of ambient $PM_{2.5}$ suggests that the IER may underestimate the attributable burden due to differences in the shape of the risk function and additional diseases not currently included in the GBD (Burnett et al. 2018; Lelieveld et al. 2019). The risk function for ozone exposure is derived from a meta-analysis for COPD based on data from cohort studies in the United States, Canada, and the United Kingdom. Increasing exposure and the updated risk function for ozone brought the number of deaths worldwide from ambient ozone in the most recent iteration of GBD to more than 471 (UI 177–767) thousand (Stanaway et al. 2018).

Limitations and potential approaches. Although existing approaches provide critical air pollution estimates to inform policy-making, opportunities exist to facilitate targeted research—from within IHME and from the broader EH community—to improve burden estimates (see Appendix 1), particularly with respect to the response relationships in high- and low-exposure environments, the potential joint effects of exposures, the IER, differential toxicity, and source attribution.

Additional epidemiological studies in both high and low air pollution regions are needed to support estimation of relative risk across the global range of exposure and more accurately estimate TMRELs. Currently, most data come from studies conducted in high-income countries (HICs), which have lower air pollution in comparison with LMICs. The use of secondhand and active smoking data to help inform the shape of the risk curve at the high end of the $PM_{2.5}$ exposure range is suboptimal; cohort studies in countries at the upper end of the ambient exposure range are needed to minimize extrapolation and reliance on smoking data. As air pollution declines to even lower levels in HICs, studies of the effects of these exposures are also needed to more accurately and precisely estimate the magnitude and shape of exposure response relationships. Recently published Chinese studies (Yin et al. 2017), alternative exposure–response functions (Burnett et al. 2018), and on-going research on effects of exposure to low levels of ambient air pollution by the HEI have begun to fill these needs. Further work should be encouraged and supported. Evaluation of the shape of the concentration–response relationship at low concentrations is currently an area of active research (Di et al. 2017; Pinault et al. 2016).

Additional efforts could further refine estimates of the independent and joint effects attributable to household and ambient air pollution (Turner et al. 2014; Turner et al. 2017; Yu et al. 2018). For settings with widespread household burning of solid fuels for cooking and heating, periodic exchange between household and ambient exposures results in substantial interdependence. The recent revisions to the GBD methods described above could be additionally refined by quantifying the extent of overlap between household and ambient concentrations, which would require estimates of dirty fuel use and indoor ventilation at a spatial resolution equivalent to the ambient air pollution exposure data. Data sets like the Demographic and Health Surveys (DHS) or Multiple Indicator Cluster Surveys (MICS) contain these variables or proxies, and there are established methods for producing estimates at the current resolution of GBD $PM_{2.5}$ estimates (Graetz et al. 2018). Similar approaches could also be extended to address the overlap between exposure to ambient $PM_{2.5}$ and secondhand smoke, another important EH risk factor whose attributable burden is estimated using the IER approach.

The IER is a central aspect of the GBD estimations. A key assumption of the IER, and consistent with assessments conducted by the WHO (WHO Regional Office for Europe 2013) and the U.S. Environmental Protection Agency (U.S. EPA) (U.S. EPA 2018), is that the magnitude of risk is a function of $PM_{2.5}$ mass alone. In other words, all particles are equally toxic on a per-unit mass basis, regardless of composition or source. Although some data suggest that $PM_{2.5}$ may exhibit differential toxicity depending on combustion source (Thurston et al. 2016; Zanobetti et al. 2009), there is currently insufficient evidence to move beyond the assumption of equitoxicity or create source-specific exposure–response functions (Lippmann et al. 2013; Pope et al. 2018; Stanek et al. 2011). Further research by the broader EH community, to be leveraged by the GBD, is needed to help advance this area. Although it would require both additional evidence and methodological work to develop separate exposure–response functions for different profiles of PM and more accurately characterize mixtures across the world at sufficient resolution, a binned approach, whereby prototypical air pollution profiles are developed to represent the most common mixtures, may represent a manageable path forward. Prioritization of this effort should be based on the size of the exposed populations; for example, windblown mineral dust (e.g., from deserts) constitute a large fraction of PM in many parts of the world, Evidence is emerging to indicate that such exposures increase mortality risk; however, the relative toxicity of desert dust in comparison with other PM is uncertain (Karanasiou et al. 2012).

An alternative approach to obtaining source-specific burden estimates is based on emissions and chemical transport modeling in which the fraction of the total particle mass attributable to a given source or sector is used to apportion exposure and, ultimately, burden (Conibear et al. 2018). This approach has been applied to estimate the burden of disease attributable to major

sources globally (Lelieveld et al. 2015), including in India and China (GBD MAPS Working Group 2016, 2018). Expansion of this analysis to other regions is feasible and would provide knowledge that is critical to identifying the specific sources whose control could contribute most to reductions in exposure and improvements in population health.

Lead. Impacts of lead exposure on disease and death have been included in the GBD since 2003. These data have included estimates of lead's impacts on intellectual impairment (in terms of IQ decrements meeting criteria for intellectual disability, defined as an IQ below 85 points), on cardiovascular outcomes mediated through increases in blood pressure (Ezzati et al. 2004; Fewtrell et al. 2004), and on the development of chronic kidney disease (Bowe et al. 2018). The primary exposure metric used previously had been log-normal distributions of blood lead concentrations (B-Pb) across populations based on published studies. Since GBD 2016, ensemble modeling techniques (which synthesize the results of different analytical models) have been used to find an optimal global distribution shape by fitting a variety of distributions to the available blood lead and generating a weighted average of those distributions based on fit. GBD uses spatiotemporal Gaussian process regression (ST-GPR) to estimate B-Pb for all age groups, locations, and years. Where no data are available, estimates are informed by data from neighboring countries, and four covariates: *a*) use of leaded gasoline, *b*) numbers of two- and four-wheeled vehicles per capita, *c*) proportion of each location's population living in an urban area, and *d*) the sociodemographic index (IHME, http://www.healthdata.org/taxonomy/glossary/socio-demographic-index-sdi) of the location (Stanaway et al. 2018). Data from primarily urban or rural locations (these data did not reflect the nationwide urban/rural distribution) were adjusted to more accurately reflect the expected national-level mean B-Pb levels, using the country's urbanicity as a covariate when estimating the adjustment. The GBD currently uses a B-Pb TMREL of 2.0 μg/dL.

The risk of intellectual disability associated with lead exposure is based on a pooled analysis of exposure–IQ decrement relationships in which losses of IQ points are converted into estimated numbers of cases of intellectual disability. Intellectual disability is classified into five levels of severity and associated disability weights (DW) are assigned: borderline (IQ 70 to 85; DW = 0.011), mild (IQ 50 to 69; DW = 0.043), moderate (IQ 35 to 49; DW = 0.1), severe (20 to 34; DW = 0.16), and profound (IQ 0 to 19; DW = 0.2).

The association between lead and blood pressure was initially based on meta-analyses involving large cross-sectional studies of lead and blood pressure, such as the U.S. Second National Health and Nutrition Examination Survey (NHANES II). The distribution of population B-Pbs linked to increased blood pressure was then combined with the relative risk for each blood pressure level to calculate the attributable fraction of cardiovascular disease (CVD) attributable to lead. These approaches were modified for GBD 2010 to estimate the association between bone lead levels and CVD outcomes as meditated through increases in systolic blood pressure. This modification was based on recent research demonstrating that bone lead levels, an indicator of exposure accumulated over decades that can now be measured noninvasively using K-X-ray fluorescence, are better than B-Pb at predicting CVD and other adult health outcomes (Navas-Acien et al. 2008) (Hu et al. 1998). Because population data on bone lead levels were available for only a few countries, bone lead levels were calculated by estimating secular trends in blood lead levels in each geography, integrating blood lead levels over time to generate a cumulative blood lead index (CBLI) metric, and applying an empirically derived factor to convert CBLI into bone lead levels (Hu et al. 2007). National and subnational data on blood lead levels are available in most countries, but many, particularly in Africa and Central Asia, continue to lack data (see Figure 2).

The most recent iteration of the GBD has estimated that global lead exposure is responsible for 2.5 million DALYs from intellectual disability, 1.3 million DALYs from chronic kidney disease, and 20.6 million DALYs from CVD (Stanaway et al. 2018).

Limitations and potential approaches. Despite its expansion to include full and borderline intellectual disability, the DALY-based GBD accounts for only a subset of the intellectual impairment due to lead. Thus, whereas GBD calculates incremental loss of IQ from lead exposure beginning at a TMREL of 2 μg/dL (Stanaway et al. 2018), contributions to DALYs are counted only for those individuals whose loss of IQ results in an IQ score below 85. However, as discussed recently by Bellinger (Bellinger 2018), decrements in IQ across the entire distribution result in reduced economic productivity, lowered educational potential, and diminished well-being. In addition, when the process of assigning DWs within the GBD Study changed in 2010, the weights for intellectual disability decreased across the board, with, for example, the disability weight associated with mild impairment (IQ 50–69) downgraded from 0.29 to, as noted above, 0.043, an 85% reduction (WHO 2013). This decrease may reflect discordance with respect to definitions of health and perspectives on whether intellectual impairment should be considered a disease.

How might GBD methods be modified to better capture the full impact of lead exposure on individual and societal health (Appendix 1)? It could be argued that any approach should consider the extent to which exposure limits an individual's educational, occupational, and social potential throughout life (Bellinger 2018). Because these outcomes extend beyond traditional (medically based) notions of health and disease, an alternative method would be to use a human capital approach (Becker 1962), which assigns monetary value to direct and indirect costs to individuals and society due to adverse outcomes, including but not limited to health. IHME has recently produced estimates of measured and expected human capital across the globe (Foreman et al. 2018; Lim et al. 2018), through the creation of an index that integrates data on educational attainment (average years of education), education quality or learning (test scores), functional health (conditions linked to productivity, including poor growth, anemia, cognitive impairment, sensory impairments, certain common infectious diseases), probability of survival to age 5, and of survival from age 20 to age 64. Using this approach, the impact of lead could be applied to educational attainment and learning, given the substantial literature linking IQ to years of schooling and extensive research documenting associations between blood lead and standardized test scores (Amato et al. 2012; Blackowicz et al. 2016; Liu et al. 2013; Magzamen et al. 2013; McLaine et al. 2013; Zhang et al. 2013). Alternatively, a hybrid approach could build on the existing GBD framework, quantifying the subclinical effects of developmental neurotoxicants and then assigning a monetary value to these effects. This strategy has been used to quantify the economic effects of population exposures to lead (Grosse et al. 2002) and EDCs (Trasande et al. 2016). Monetary values could be based on the Value of a Life Year (VOLY) (Desaigues et al. 2011), adjusted for purchasing-power parity (PPP) (Taylor 2003).

GBD estimates of the burden of CVD attributable to lead currently include the effects of lead on CVD only as they are mediated through blood pressure, with a threshold for effects beginning at B-Pbs of 5 μg/dL. However, a recent study using updated NHANES data demonstrated that an increase in B-Pbs

from 1.0 μg/dL to 6.7 μg/dL was associated with an increase in all-cause mortality even after adjusting for blood pressure, with effect magnitudes several multiples greater than current GBD estimates (Lanphear et al. 2018). Similarly, a community-based prospective study of men in Boston, Massachusetts, found that even after adjusting for hypertension and other covariates, cumulative lead was associated with increased risk of CVD mortality (Weisskopf et al. 2009). That lead likely has a direct effect on the cardiovascular system apart from effects on blood pressure is supported by numerous mechanistic studies demonstrating direct effects on heart muscle function, atherosclerosis, and the heart's conduction system (Navas-Acien et al. 2007). These findings suggest that the GBD may need to additionally account for evidence indicating that lead's effects on CVD are exerted directly, as well as through blood pressure.

The current TMREL of 2.0 μg/dL should also be reconsidered. Research suggests that preindustrial B-Pb levels were likely well below 1 μg/dL (Flegal and Smith 1992; Patterson et al. 1991; Smith and Flegal 1992). Mean B-Pb levels in some populations have recently declined to below 1 μg/dL: For example, the latest published B-Pb levels among participants of the U.S. NHANES showed a mean level of 0.84 μg/dL in the period 2013–2014 (Tsoi et al. 2016). In addition, the most recent research on B-Pb–IQ and B-Pb–CVD relationships demonstrates a slope that is steepest and begins at the lowest measurable levels (down to 1 or 2 μg/dL) (Evens et al. 2015; Hu et al. 2006; Kordas et al. 2006; Lanphear et al. 2005; Schneider et al. 2003; Wasserman et al. 2003). Lowering the TMREL from 2 to 1 μg/dL therefore deserves serious consideration.

Finally, despite being one of the most studied EH risk factors, B-Pb data are sparse or absent in dozens of countries, particularly in Africa and Asia, where development and industrialization are occurring rapidly (Figure 2). Although current exposure estimation methods are laudable, the potential exists to further expand the consortium of GBD collaborators to include researchers with unpublished data [such as national surveillance data on over 25,000 blood lead levels in China (Yan 2018)] and researchers who could add B-Pb measurement to existing or future population-based surveys. In the meantime, additional strategies could be adopted to improve B-Pb estimates.

Methods for Grading Evidence and Exposure Assessment, and Prioritizing EH Risk Factors

Many well-established EH risk-outcome pairs are not included in the GBD. Examples include methylmercury and intellectual disability (Grandjean and Landrigan 2014; Trasande et al. 2005), nitrogen dioxide and asthma (Achakulwisut et al. 2019; Anenberg et al. 2018), and $PM_{2.5}$ and low birth weight (Dadvand et al. 2013; Fleischer et al. 2014). Although a main factor in the GBD's success is its rigor, impartiality, and standardization for establishing new risk–outcome pairs, there are challenges associated with incorporating new EH risk factors, as well as general limitations inherent in the GBD, that require consideration. Critical among the latter is the practical reality that the process of adding a new risk–outcome pair to the GBD is typically labor-intensive and thus undertaken only if the additional necessary resources are available. By contrast, the scope of pollution is enormous; Rusch and Hare (2014) estimated that there are 25,000–84,000 chemicals in commerce in the United States (Rusch and Hare 2014). A further issue, as noted earlier, is that most EH risk–outcome pairs cannot be assessed by RCTs, thereby placing a stronger emphasis on the results of

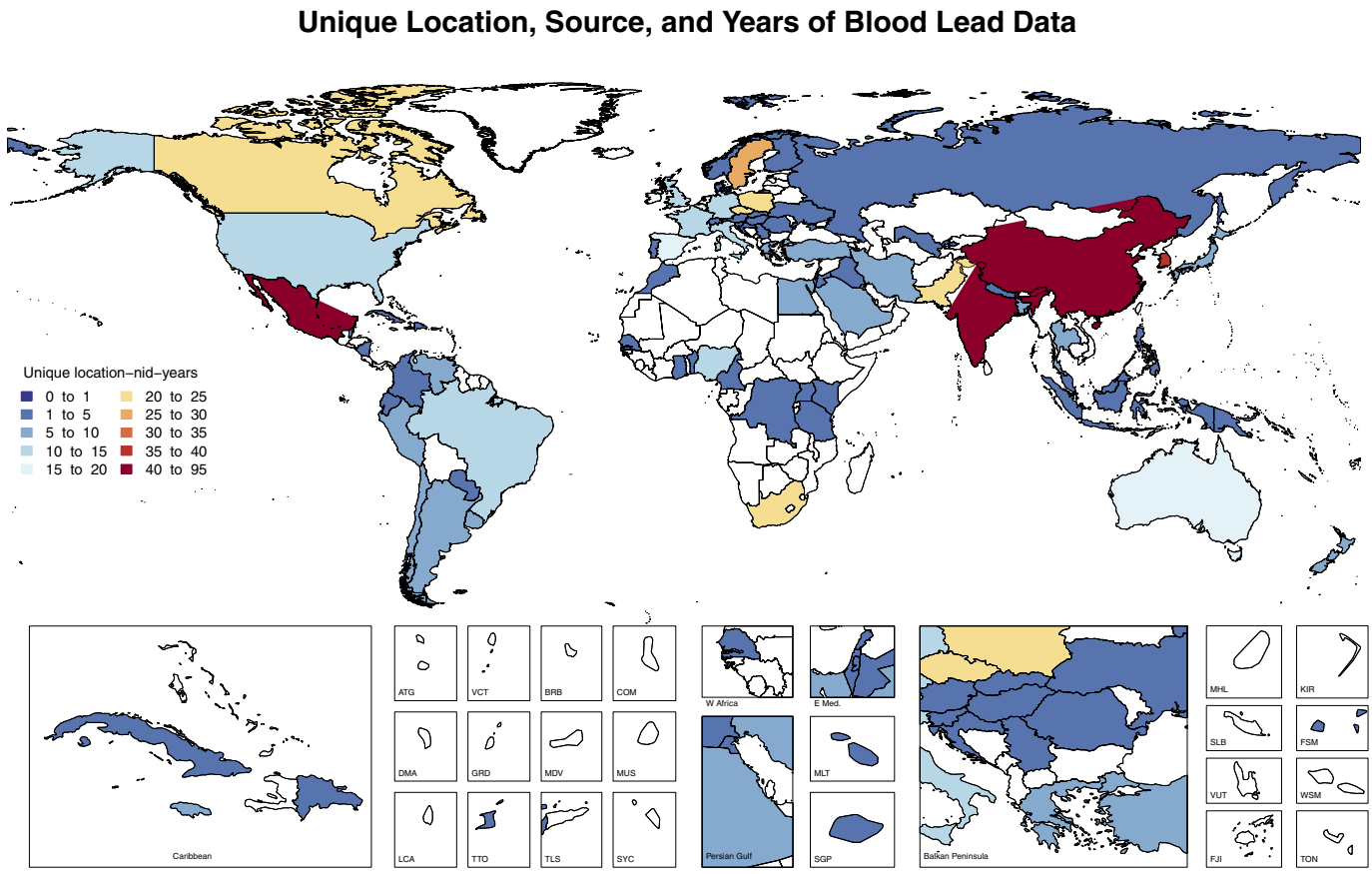

Figure 2. Map of unique country, source, and years of data on blood lead levels for the Global Burden of Disease Study (GBD) (Stanaway et al. 2018).

Table 2. Suggested examples of risk/outcome pairs for consideration by the Global Burden of Disease Study (GBD).[a]

Risk factor	Outcome[b]	Global exposure assessment available/feasible for risk factor?
Air pollution ($PM_{2.5}$, ozone, NO_2)	Dementia (Power et al. 2016)	Yes (currently in GBD) (Stanaway et al. 2018)
	Intellectual disability (Bennett et al. 2016; Clifford et al. 2016)	
	*Low birth weight (Dadvand et al. 2013; Fleischer et al. 2014)	
	*Hypertension (Brook et al. 2010)	
	*Asthma (Achakulwisut et al. 2019; Anenberg et al. 2018; Guarnieri and Balmes 2014; Khreis et al. 2017)	
Arsenic (nonoccupational)	Intellectual disability (Grandjean and Landrigan 2006)	Regional assessments have been conducted (e.g., Bangladesh (Smith et al. 2000); Latin America (Bundschuh et al. 2012)
	Lung cancer (IARC Working Group 2012)	Needs to be scaled and modeled for global coverage
	Bladder cancer (IARC Working Group 2012)	
	Skin cancer (IARC Working Group 2012)	
Lead	*Cardiovascular disease (direct effects; *low-level exposures*) (Lanphear et al. 2018)	Yes (currently in GBD) (Stanaway et al. 2018)
Methylmercury	Intellectual disability (Grandjean and Landrigan 2006)	Yes (Basu et al. 2018)
Organophosphate pesticides	Intellectual disability (Grandjean and Landrigan 2006)	Included in national and regional biomonitoring (CDC 2019) Needs to be scaled and modeled for global coverage
Phthalates	BMI (Attina et al. 2016; Legler et al. 2015)	Included in national and regional biomonitoring (CDC 2019)
	Diabetes (Attina et al. 2016; Legler et al. 2015)	Needs to be scaled and modeled for global coverage
	Infertility (Attina et al. 2016; Hauser et al. 2015)	
Per- and polyfluoroalkyl substances	BMI (Liu et al. 2018)	Included in national and regional biomonitoring (CDC 2019)
	Low birth weight (Johnson et al. 2014)	Needs to be scaled and modeled for global coverage
Polybrominated diphenyl ethers	Intellectual disability (Grandjean and Landrigan 2006)	Included in national and regional biomonitoring (CDC 2019) Needs to be scaled and modeled for global coverage
Polychlorinated biphenyls	Intellectual disability (Grandjean and Landrigan 2006)	Included in national and regional biomonitoring (CDC 2019)
	Melanoma (IARC 2016)	Needs to be scaled and modeled for global coverage

[a]Not comprehensive; selected examples only.
[b]Some of the outcomes listed here (e.g., hypertension, BMI, low birth weight) are actually risk factors for outcomes in the GBD rather than outcomes themselves. Thus, future modeling would be conducted as mediation analyses, evaluating how, for example, low birth weight mediates the association between an EH exposure and an established GBD outcome.
*Indicates consideration for inclusion in GBD2019.

observational studies and also raising the issue of whether evidence from animal and *in vitro* studies deserve consideration in the GBD.

Nomination process for EH risk factors. The current process for including new risk–outcome pairs is based on input from collaborators, followed by considering available exposure information, systematic reviews, and evidence scoring, and then approval from the GBD Scientific Council (IHME 2016). With the creation of the GBD-PHI, we propose forming an EH Risk Factors Nomination Working Group (EH Working Group) to work in partnership with the GBD to ensure a systematic process for considering data to support the inclusion of new EH risk–outcome pairs and updated information (including new disease linkages) for existing risk factors. This group would be responsible for reviewing literature on EH exposures and risk–outcome pairs and nominating selected pairs for consideration. As a first step, the EH Working Group could identify candidates from existing classifications or listings from authoritative bodies. Examples include International Agency for Research on Cancer (IARC) monographs, the European Chemicals Agency (ECHA) Candidate List of substances of very high concern, the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) reports, California's Proposition 65 listings, U.S. EPA's Integrated Risk Information System (IRIS) reports, and Project TENDR's consensus statement (Bennett et al. 2016). We recommend prioritizing new risk factors based on strength of evidence of causality with one or more health outcomes, the size of exposed populations, the feasibility of global exposure estimation, and predicted trends in exposures and relevant diseases. Linking an existing risk factor, for which the GBD already has exposure information, to a new disease is easier and may be a more practical starting point with respect to EH expansion. Table 2 depicts a nonexhaustive list of risk factor–disease pairs that may be ready for consideration based on the criteria above.

Causality and evidence scoring criteria. After nomination, EH risk–outcome pairs would be subject to the same criteria used for other risk–outcome pairs in the GBD. To date, GBD has used the World Cancer Research Fund evidence grading system (World Cancer Research Fund/American Institute for Cancer Research 2018), with "convincing" or "probable" evidence as a requirement for inclusion. Causal criteria include consideration of study design, relative risk, dose–response relationship, biological plausibility, and analogy (Stanaway et al. 2018). GBD's current system gives greatest weight to RCTs, which, for ethical and practical reasons, are only possible for very few EH exposures (e.g., clean cook stoves, energy interventions to reduce household air pollution) (Smith et al. 2011; Allen et al. 2015). Observational studies are the primary epidemiologic method for EH. Careful design can mitigate many concerns about residual confounding even in the absence of *a priori* randomization, such as the application of causal modeling techniques (Rothman et al. 2008; Zeger et al. 2000). In addition, the U.S. NTP and others have adapted systematic review frameworks to assess hazards that, in addition to epidemiological studies, consider a range of experimental animal and mechanistic data to reach conclusions (Rooney et al. 2014; Woodruff and Sutton 2011). We see opportunities for collaboration between IHME and NTP to advance the use of systematic review in environmental health. GBD is in the process of implementing a quantitative data-driven evidence scoring approach that will likely yield different categories of evidence for risk–outcome pairs, leading to a series of burden estimates based on different levels of evidence.

Finally, given concerns about the influence of funding on study findings (Bero 2017; Friedman and Friedman 2016; Gennaro and Tomatis 2005; Huff 2007; Lundh et al. 2017), any assessment of data quality and causality in EH should include consideration of conflict of interest. The recently developed Navigation Guide systematic review method includes "conflict of interest" as a domain in its risk of bias assessment (Woodruff and Sutton 2014), and we would encourage a similar approach for the GBD.

Global exposure assessment. To best inform the GBD, exposure measurements need to capture variability by sex, age,

seasonality, and national/subnational geography, so that exposure models can calculate age–sex, regional, and time-of-year–specific estimates of mortality or DALYs. Although it is challenging to estimate exposure to many environmental risk factors, air pollution has fairly robust exposure estimates worldwide. In the most recent iteration of the GBD, data coverage for subnational geographies was as follows: ozone pollution data: 100% (although some of the ozone data are based on chemical transport models); ambient PM: 58%; and household air pollution from solid fuels: 85.5% (Stanaway et al. 2018). Additional tools that could be leveraged in the future include regional emissions inventories (Kurokawa et al. 2013), low-cost samplers and sensors (Austin et al. 2015; Nieuwenhuijsen et al. 2015; O'Connell et al. 2014), and the use of high-resolution satellite imagery (Garcia-Saenz et al. 2018).

Estimating global exposure to lead is more difficult, however, and emblematic of the challenges presented by many other EH exposures. Population exposure to lead in the mid- to late-20th century was dominated by inhalation of leaded gasoline, and B-Pb was accurately modeled using data on measured air lead levels, sales of leaded gasoline, and traffic density. However, the current predominant sources of lead exposures are mostly due to contamination of food, water, dust, and soil, which are more challenging to model. Thus, it is necessary to rely on population-specific B-Pb. However, as noted earlier in the lead case study, in the most recent iteration of the GBD, B-Pb data were lacking for many countries in Africa and central Asia; moreover, global data were available for only 39.6% of the subnational geographies (Forouzanfar et al. 2016), forcing the GBD to rely on data derived from exposure to leaded gasoline, likely leading to biased estimates where other routes and sources of exposure are not considered (i.e., food, water, occupational exposures). An example is India, which phased lead out of gasoline in 2000, but recent data indicate continuing high levels of B-Pb in children (Chaudhary et al. 2018).

Going forward, innovations will be needed on multiple levels to address the challenge of assessing global exposures for new pollutants being considered for entry into the GBD, with particular challenges posed by the lack of data for most exposures of concern, especially in LMICs. Some of the innovations could be technological, with the development of new, low-cost tools for measuring pollutants in biological as well as environmental media. Other innovations may involve diversifying sources of data. For example, with respect to methylmercury, arsenic, trace metals, pesticides, PBDEs, and other exposures found to occur mainly via diet (Schecter et al. 2006; Williams et al. 2007; Ysart et al. 2000), extrapolations could be made from market-basket surveys (Radwan and Salama 2006) and drinking water assessments (Villanueva et al. 2017). Computational approaches should also be considered. A 2016 U.S. National Academies of Sciences report detailed the promise of modeling approaches that can aggregate information on chemical properties and emission sources with environmental fate and transport characteristics to predict near- and far-field human exposures to a large number of pollutants (National Academies of Sciences 2017a).

Perhaps the most important innovation that will be key to advancing assessment of global pollutant exposures for the GBD will be soliciting the involvement of subject-matter experts around the world (and training them where few exist). The GBD project currently involves more than 3,600 researchers in more than 145 countries. However, few of the researchers are exposure or EH scientists; and of these exposure or EH experts, there is limited representation among LMICs. Efforts have already started in this area through the promotion of GBD symposia in relevant professional societies, such as the International Society for Environmental Epidemiology (ISEE) and the International Society of Exposure Science (ISES). In addition, Landrigan et al. recently created the Global Pollution Observatory on Pollution and Health as a consortium to collect, archive, and analyze data on pollution and disease worldwide (Landrigan et al. 2018b). Such an effort will meet its promise only with the involvement of LMIC-based researchers, particularly because the Lancet Commission on Pollution and Health estimated that 92% of pollution-related mortality occurs in these regions (Landrigan et al. 2018a). The cultivation of regional expertise and engagement in this initiative will be critical not only in terms of gathering data relevant to exposures, but also in terms of providing interpretation of the data in relation to nuances such as local behaviors, industrial and social trends, and national and regional chemicals management policies. Efforts to increase EH capacity of individuals and institutions across LMICs, as well as to strengthen and help sustain regional and global networks, continue to be promoted through efforts like Fogarty International Center's GEOHealth program and Canada's IDRC EcoHealth Chairs program.

A related issue in the field of exposure is the estimation of the TRMEL. As noted earlier, a critical step in calculating the attributable burden for each risk–outcome pair is the estimation of the exposure counterfactual or TMREL. Relatively small changes in the TMREL can result in relatively large changes in the PAF, underscoring the importance of making accurate estimations. However, this can be challenging for naturally occurring pollutants, such as arsenic, or for others that have imbued the ecosystem and entered the food chain in various ways, such as mercury. Establishing a TMREL for climate-related risk factors, such as heat, will also be challenging and an area for discussion in the coming years.

Examples of Candidate EH Risk Factors for Inclusion in the GBD

Neurotoxicants. Lead is the best-studied neurodevelopmental toxicant, but there are others for which there is strong evidence and widespread exposure. Evidence is strong or rapidly accumulating for the impact of methylmercury, arsenic, polychlorinated biphenyls, polybrominated diethyl esters (PBDEs), organophosphate pesticides, and particulate air pollution on diminished cognitive function, shortened attention span, and behavioral disruption; each has been subject to systematic or similarly in-depth reviews (Bennett et al. 2016; Clifford et al. 2016; El Majidi et al. 2013; Grandjean and Landrigan 2014; Karagas et al. 2012; Lam et al. 2017; Levy 2015; Payne-Sturges et al. 2019; Sheehan et al. 2014; Tolins et al. 2014). Extensive use of these chemicals has resulted in pervasive human exposure, and virtually everyone has detectable levels of multiple neurotoxicants in their bodies (CDC 2019). Moreover, diminished cognitive function is associated with even the lowest measurable concentrations for many of these neurotoxicants (Grandjean and Landrigan 2014).

The health impacts of exposures to these other neurotoxicants should be quantified to illustrate the benefits of exposure reductions. Especially robust dose-response and exposure data have been developed for methylmercury, for example (Basu et al. 2018; Karagas et al. 2012). IHME could evaluate the effects of these exposures using the newly developed human capital index; a similar analysis was recently published for an extended group of environmental chemicals (Grandjean and Bellanger 2017). However, despite the documented neurobehavioral effects of these risk factors, limited exposure data present a challenge in developing global exposure models. For others, data may not be yet sufficient to meet the GBD's criteria for causality. Due to these limitations, none of these other neurotoxicants are currently included in the GBD. Inclusion of these and other chemicals would serve to add urgency to the need to address their public

health impacts. A phased approach to considering other neurotoxic agents could begin with an evidence-scoping phase to identify the information gaps for the major neurotoxicants listed above (e.g., the lack of exposure data or the lack of evidence to support causality). In subsequent steps, research efforts could be directed to fill the key data gaps, and individual risk–outcome pairs could be addressed in subsequent GBD reviews.

Endocrine-disrupting chemicals (EDCs). Growing evidence documents the link between EDC exposure and numerous adverse outcomes, including hormone-related cancers, infertility, reproductive dysfunction, birth defects, obesity, diabetes, and neurobehavioral disruptions (Bergman et al. 2013; Diamanti-Kandarakis et al. 2009; Gore et al. 2015). Examples of specific risk–outcome pairs, among many, include bisphenol A and childhood obesity, and benzyl-phthalates and butyl-phthalates and male infertility (Attina et al. 2016). Prior work external to the GBD highlights the enormous economic burden due to these exposures in the United States and the European Union: $340 billion and $217 billion, respectively (Attina et al. 2016; Trasande et al. 2016). Integration of these efforts into future iterations of the GBD would result in the expansion of EDC burden estimates to cover LMICs. This expansion is particularly important because LMICs are predicted to become the chief producers of synthetic chemicals, many of which are EDCs, by 2030 (OECD 2008); increased utilization and consumption in those countries are also anticipated. Additionally, given the worldwide visibility of the GBD, estimates for EDCs would provide further visibility to the concern regarding these ubiquitous exposures.

There are several challenges to incorporating EDCs into the GBD; we highlight selected examples here. First, there is disagreement about the definition and criteria for an *adverse effect* in the context of the endocrine system (Woodruff et al. 2008; Zoeller et al. 2012; Zoeller et al. 2014). These debates are in some ways analogous to the discussion of lead and IQ decrements, because some EDC-related changes may be considered adverse even without reaching thresholds based on clinical constructs for apical end points. Second, much of the data on EDCs are generated from *in vitro* and *in vivo* studies; in addition, methods for integration of this evidence into the GBD decision-making process are not well defined, despite this being an active area of research (National Academies of Sciences 2017b; Vandenberg et al. 2016). Additionally, because there is still much uncertainty about the health effects of some EDCs, their incorporation into the GBD may prompt the need to expand the estimation process to allow for differing tiers of certainty.

Another challenge is obtaining robust exposure estimates for EDCs across the globe. Nevertheless, even with imperfect exposure measurements and uncertainties in risk functions, the addition of these and other EH risk factors is crucial given the large burden estimations developed by other groups as cited above; an important aspect is that, as stated in the GBD Protocol, "an uncertain estimate, even when data are sparse or not available, is preferable to no estimate because no estimate is often taken to mean no health loss from that condition" (IHME 2018). Although some degree of uncertainty is acceptable, we also recognize that data to inform models must be adequate to produce estimates that are credible and provide enough certainty to be useful to the public health community and policy makers. To this end, we encourage further research to evaluate EDC exposure levels around the world.

Special Cases of Climate and Climate Change

Climate change presents a challenge for the GBD, as it cannot easily be captured as a discrete exposure but is instead represented by multiple hydrometeorological indicators. Unlike other exposures, there is no theoretical minimum future climate change exposure that can be attained, and it is unclear what the baseline level for climate risk should be, given its unique status as a constantly changing global system. Climate change–related exposures will continue to increase in the next few decades, no matter the extent of reductions of greenhouse gas emissions. For present and future climate-related risks, the risk–outcome pathways (e.g., undernutrition, malaria, diarrheal disease, and injury) are often indirect, making attribution challenging.

Because climate-related health impacts are closely tied with local mediating factors, the same hydrometeorological events affected by climate change may have very different consequences within and between locations and populations, making it challenging to extrapolate health outcomes in low-income settings from studies conducted in higher-income settings, an issue common to many environmental exposures. Although researchers have considerable experience with projecting the magnitude and pattern of certain climate-sensitive health outcomes (such as mortality associated with heat or malaria) at local to international geographic scales (Ebi et al. 2018), projecting other climate-sensitive health outcomes, such as the disease burden associated with climate-driven conflict or migration, is more challenging. GBD incorporated a limited set of climate risks in its 2000 analysis (McMichael et al. 2004) but has opted not to make attributions of climate risk in recent reports, in part because of the aforementioned challenges. Nevertheless, given the importance of estimating the disease burden from climate-related risk factors and demand from health ministries for such estimates, the GBD team has taken a first step to robustly estimating health impacts associated with climate change by beginning to incorporate risks related to suboptimal ambient temperature exposure, a process that is currently ongoing and might be expanded to include scenario-based projections.

A variety of climate-sensitive risk–outcome pair additions and modifications might be considered in future iterations of the GBD. For example, there is a well-documented association between ambient temperature and ground-level ozone formation, as well as growing evidence for temperature-driven increases in $PM_{2.5}$ in drier regions, both of which are associated with increased morbidity and mortality (Achakulwisut et al. 2018; Orru et al. 2013). In addition, higher carbon dioxide (CO_2) concentrations are associated with reduced micronutrients, protein, and B vitamins in staple crops, particularly wheat and rice (Zhu et al. 2018). These trends may exacerbate micronutrient deficiencies that are associated with a variety of physical and cognitive ailments (Bailey et al. 2015). Other risk–outcome pairs could be incorporated into future iterations of the GBD, including those associated with risks, such as precipitation changes, and outcomes, such as injuries, diarrheal disease, undernutrition, cardiovascular disease, and mental health, among others (Smith et al. 2014). Moreover, risks currently in the GBD, such as extreme weather events, will likely require attribution to climate change as the science becomes more robust. In addition, climate-related risk factors affect upstream drivers of health and welfare outcomes, including economic productivity, fertility, migration, and governance capacity. Altogether, these interconnected relationships present potentially far-reaching consequences for global health.

Modeling challenges: Aeroallergens and asthma as an example. Many diseases included in the GBD have some climate sensitivity that is not currently captured, sometimes as a result of data and modeling limitations. Multiple risk factors map to each outcome, and data are not of sufficient quality or spatiotemporal resolution to characterize the attributable burdens associated with each individual driver. An example is asthma associated with aeroallergens. Climate change is increasing allergenic pollen exposure and thus could increase the burden of allergic disease.

Aeroallergens are associated with allergic rhinitis, allergic asthma, and other conditions, and both allergic asthma development and asthma exacerbations are driven by aeroallergen exposure. Climate change has increased the length of the pollen season for certain allergens in North America above 44°N by 2 to 4 wk since 1995 (Ziska et al. 2011). However, relatively few studies have documented the dose–response relationships between pollen seasonality or magnitude and specific health outcomes. One study suggests moderate and severe climate change could increase oak pollen season length and associated asthma emergency department visits in the eastern United States by 5% and 10%, respectively, by 2090, translating into tens of thousands of pollen-related asthma emergency department visits (Anenberg et al. 2017). Although allergic disease is not included as a specific outcome in the GBD, asthma caused 23.7 million DALYs in 2016, up to half of which may be attributed to allergies (Galán et al. 2010; Pearce et al. 1999). Thus, the DALY burden of climate-induced changes in pollen-season length and intensity could be substantial. Nevertheless, attributing changes in allergy burden to climate change is challenging, given limitations in risk factor (i.e., aeroallergen) and outcome (i.e., allergic asthma) data, as well as a paucity of robust studies that might support dose–response characterization for this risk–outcome pair. This uncertainty highlights a need for funders to the support collection of data to facilitate modeling of this climate-sensitive outcome.

Climate projections. An important goal relates to modeling the possible consequences of climate change on the future burden of climate-sensitive health outcomes. This modeling is particularly important for decision-makers because the consequences of climate change, such as exposure to airborne PM from wildfires and soil dust, are likely to increase considerably in the coming decades. Modeling needs to consider not just changes in climate-related hazards and population exposure to these hazards, but also factors that affect sensitivity to the exposures and the capacity to manage changing exposures, such as changes in population distribution and investment in building climate-resilient health systems (Sellers and Ebi 2017).

The GBD is currently developing scenario-based forecasting models for disease burdens, which will require years of incremental improvements (Foreman et al. 2018). The current iteration of this forecasting model does not explore the health effects of climate change, although we believe this framework can be extended to incorporate these impacts. Such an extension will likely require incorporating feedbacks from climate shocks onto sociodemographic drivers, estimating the health impacts associated with adaptation and mitigation measures, as well as exploring potential health impacts associated with events lacking in historical precedents, such as sea-level rise.

To facilitate model development, we suggest convening a broad range of climate and health experts in the natural and social sciences to advise this work, including experts researching thermal extremes, vector-borne disease, climate and pollution, undernutrition, sea-level rise, migration, and other relevant subject areas. These experts would help elucidate the global burden of disease related to climate change in four ways: *a*) by estimating the climate change–attributable impact on climate-sensitive health outcomes that are in the GBD but do not disaggregate upstream drivers such as climate change (e.g., malaria and waterborne diseases); *b*) by tracking changes over time in dose–response relationships for climate-sensitive risk–outcome pairs and updating models accordingly; *c*) by evaluating the addition of new risk–outcome pairs to incorporate into future GBD projections as evidence builds; and *d*) by examining the impact of climate-change mitigation policies on health effects, as is currently done by GBD for policies related to the SDGs (Lozano et al. 2018). Finally, GBD should seek to harmonize its forecasts with other established methods for estimating how different development scenarios, including projections of demographic and socioeconomic change, could interact with climate change to modify projected health burdens, such as the Shared Socioeconomic Pathways (Sellers and Ebi 2017).

Conclusion

The GBD-PHI is a recently emerged virtual initiative being advanced by a community of scientists who come from a diverse array of disciplines but who are focused on the task of elucidating the true environmental footprint on the global burden of disease, disability, and impaired human capital. The ultimate aim is to provide policymakers with the informational tools for reducing and preventing these impacts as each country and region strives to meet the SDGs. As the initiative gets underway, this paper aims to highlight some of the key challenges and opportunities for enhancing the characterization of EH risk factors in the GBD (Appendix 1). Although air pollution and lead are already included in these analyses, the limitations highlighted above suggest that several specific enhancements could further improve the accuracy and utility of these globally influential estimates.

Collaboration from within the EH community, including efforts to leverage existing research, can expedite and facilitate the incorporation of new risk–outcome pairs. Ancillary studies producing global or region-specific burden estimates for new EH risk–outcome pairs using methods closely aligned with the GBD can provide the scientific rationale for inclusion. Investigators who have developed a set of global exposure estimates can combine these with either published or de novo meta-analytic concentration–response summaries and GBD baseline disease incidence information to develop proof-of-concept global disease burden estimates. An example is the recent quantification of NO_2-attributable pediatric asthma (Achakulwisut et al. 2019). It would be important for analyses to align exposure–response functions with the specific outcome classifications currently included in the GBD or to develop methods to link GBD outcomes to other outcomes used in epidemiological studies. Further, ancillary studies may provide more in-depth insight into the role of pollution sources or the potential benefits of various policy scenarios on disease burden, as has become common with respect to air pollution (GBD MAPS Working Group 2018; Zhang et al. 2017; Zhao et al. 2018).

To generate quantitative estimates for the GBD, adequate data must exist to credibly estimate exposure to the risk factor for all countries and timeframes included. Such data do not currently exist for most EH risk factors. We predict that the proliferation of new technologies and the sources of "Big Data" on population health scales will improve exposure assessment to support the addition of new EH risk–outcome pairs in future iterations of the GBD, and we encourage research to accelerate this process (Hu et al. 2017). The GBD-PHI can support progress by building collaborations with EH colleagues conducting such research and through partnerships with, among others, the U.S. National Institute of Environmental Health Sciences (NIEHS), the WHO, the United Nations Environment Programme (UNEP), the Intergovernmental Panel on Climate Change (IPCC), ISEE, ISES, the Global Observatory on Pollution and Health, and the HEI. GBD scientists can play a role by highlighting key gaps in exposure data to inform relevant research.

GBD estimates are influential at the local, subnational, national, and international levels, and they help all governments evaluate comparative risks and make evidence-based decisions to improve public health. These estimates have an especially important role in LMICs, which often experience particularly high burdens from EH exposures, and for countries that lack the resources to estimate risk exposure and risk-attributable burden internally.

As the GBD expands its breadth with regard to EH risk–outcome pairs, its results can facilitate expanded economic analyses and policy assessments. Further consideration of the range of effects on human capital, including both education and health, is crucial. Only with adequate quantification of the adverse impacts of a broad range of EH exposures will governments and policy makers be positioned to make well-informed decisions to appropriately allocate resources for public health. These efforts, which will be further described in a follow-up manuscript, are particularly important for reaching ambitious global targets, such as the SDGs, and for more accurate quantification of the risks and benefits of pollution mitigation and prevention efforts.

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References

Achakulwisut P, Brauer M, Hystad P, Anenberg SC. 2019. Global, national, and urban burdens of paediatric asthma incidence attributable to ambient NO_2 pollution. Lancet Planet Health 3(4):e166–e178, PMID: 30981709, https://doi.org/10.1016/S2542-5196(19)30046-4.

Achakulwisut P, Mickley LJ, Anenberg SC. 2018. Drought-sensitivity of fine dust in the US Southwest: implications for air quality and public health under future climate change. Environ Res Lett 13(5):054025, https://doi.org/10.1088/1748-9326/aabf20.

Allen RW, Barn PK, Lanphear BP. 2015. Randomized controlled trials in environmental health research: unethical or underutilized? PLoS Med 12(1):e1001775, PMID: 25562846, https://doi.org/10.1371/journal.pmed.1001775.

Amato MS, Moore CF, Magzamen S, Imm P, Havlena JA, Anderson HA, et al. 2012. Lead exposure and educational proficiency: moderate lead exposure and educational proficiency on end-of-grade examinations. Ann Epidemiol 22(10):738–743, PMID: 22902043, https://doi.org/10.1016/j.annepidem.2012.07.004.

Anenberg SC, Henze DK, Tinney V, Kinney PL, Raich W, Fann N, et al. 2018. Estimates of the global burden of ambient $PM_{2.5}$, ozone, and NO_2 on asthma incidence and emergency room visits. Environ Health Perspect 126(10):107004, PMID: 30392403, https://doi.org/10.1289/EHP3766.

Anenberg SC, Weinberger KR, Roman H, Neumann JE, Crimmins A, Fann N, et al. 2017. Impacts of oak pollen on allergic asthma in the United States and potential influence of future climate change. GeoHealth 1(3):80–92, https://doi.org/10.1002/2017GH000055.

Attina TM, Hauser R, Sathyanarayana S, Hunt PA, Bourguignon JP, Myers JP, et al. 2016. Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. Lancet Diabetes Endocrinol 4(12):996–1003, PMID: 27765541, https://doi.org/10.1016/S2213-8587(16)30275-3.

Austin E, Novosselov I, Seto E, Yost MG. 2015. Laboratory evaluation of the Shinyei PPD42NS low-cost particulate matter sensor. PLoS One 10(9):e0137789, PMID: 26367264, https://doi.org/10.1371/journal.pone.0137789.

Bailey RL, West KP Jr, Black RE. 2015. The epidemiology of global micronutrient deficiencies. Ann Nutr Metab 66(2):22–33, PMID: 26045325, https://doi.org/10.1159/000371618.

Basu N, Horvat M, Evers DC, Zastenskaya I, Weihe P, Tempowski J. 2018. A state-of-the-science review of mercury biomarkers in human populations worldwide between 2000 and 2018. Environ Health Perspect 126(10):106001, PMID: 30407086, https://doi.org/10.1289/EHP3904.

Becker GS. 1962. Investment in human capital: a theoretical analysis. J Pol Econ 70(5, Part 2):9–49, https://doi.org/10.1086/258724.

Bellinger DC. 2018. Applying methods of the global burden of diseases, injuries, and risk factors study to developmental neurotoxicants: a commentary. Environ Health 17(1):53, PMID: 29866119, https://doi.org/10.1186/s12940-018-0397-7.

Bennett D, Bellinger DC, Birnbaum LS, Bradman A, Chen A, Cory-Slechta DA, et al. 2016. Project TENDR: targeting environmental neuro-developmental risks the TENDR consensus statement. Environ Health Perspect 124(7):A118–A122, PMID: 27479987, https://doi.org/10.1289/EHP358.

Bergman Å, Heindel JJ, Jobling S, Kidd KA, Zoeller RT. 2013. *State of the Science of Endocrine Disrupting Chemicals 2012: An Assessment of the State of the Science of Endocrine Disruptors Prepared by a Group of Experts for the United Nations Environment Programme (UNEP) and WHO*. Geneva: World Health Organization.

Bero L. 2017. Addressing bias and conflict of interest among biomedical researchers. JAMA 317(17):1723–1724, PMID: 28464166, https://doi.org/10.1001/jama.2017.3854.

Blackowicz MJ, Hryhorczuk DO, Rankin KM, Lewis DA, Haider D, Lanphear BP, et al. 2016. The impact of low-level lead toxicity on school performance among Hispanic subgroups in the Chicago Public Schools. Int J Environ Res Public Health 13(8):774, PMID: 27490560, https://doi.org/10.3390/ijerph13080774.

Bowe B, Xie Y, Li T, Mokdad AH, Xian H, Yan Y, et al. 2018. Changes in the US burden of chronic kidney disease from 2002 to 2016: an analysis of the Global Burden of Disease Study. JAMA Netw Open 1(7):e184412, PMID: 30646390, https://doi.org/10.1001/jamanetworkopen.2018.4412.

Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121(21):2331–2378, PMID: 20458016, https://doi.org/10.1161/CIR.0b013e3181dbece1.

Bruce N, Dherani M, Liu R, Hosgood HD, Sapkota A, Smith KR, et al. 2015. Does household use of biomass fuel cause lung cancer? A systematic review and evaluation of the evidence for the GBD 2010 study. Thorax 70(5):433–441, PMID: 25758120, https://doi.org/10.1136/thoraxjnl-2014-206625.

Bundschuh J, Litter MI, Parvez F, Román-Ross G, Nicolli HB, Jean JS, et al. 2012. One century of arsenic exposure in Latin America: a review of history and occurrence from 14 countries. Sci Total Environ 429:2–35, PMID: 21959248, https://doi.org/10.1016/j.scitotenv.2011.06.024.

Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA 3rd, et al. 2018. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. PNAS September 18, 2018. 115(38) 9592–9597, https://doi.org/10.1073/pnas.1803222115.

Burnett RT, Pope CA 3rd, Ezzati M, Olives C, Lim SS, Mehta S, et al. 2014. An integrated risk function for estimating the global burden of disease attributable to ambient fine particulate matter exposure. Environ Health Perspect 122(4):397–403, PMID: 24518036, https://doi.org/10.1289/ehp.1307049.

Centers for Disease Control and Prevention (CDC). 2019. Fourth Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, https://www.cdc.gov/exposurereport/index.html [accessed 15 May 2019].

Chang KL, Cooper OR, West JJ, Serre ML, Schultz MG, Lin M, et al. 2019. A new method (M^3Fusion v1) for combining observations and multiple model output for an improved estimate of the global surface ozone distribution. Geosci Model Dev 12(3):955–978, https://doi.org/10.5194/gmd-12-955-2019.

Chaudhary S, Firdaus U, Ali SM, Mahdi AA. 2018. Factors associated with elevated blood lead levels in children. Indian Pediatr 55(1):38–40, PMID: 28952456, https://doi.org/10.1007/s13312-018-1225-4.

Chen H, Goldberg MS, Villeneuve PJ. 2008. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. Rev Environ Health 23(4):243–298, PMID: 19235364, https://doi.org/10.1515/REVEH.2008.23.4.243.

Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. 2016. Exposure to air pollution and cognitive functioning across the life course–a systematic literature review. Environ Res 147:383–398, PMID: 26945620, https://doi.org/10.1016/j.envres.2016.01.018.

Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389(10082):1907–1918, PMID: 28408086, https://doi.org/10.1016/S0140-6736(17)30505-6.

Conibear L, Butt EW, Knote C, Arnold SR, Spracklen DV. 2018. Residential energy use emissions dominate health impacts from exposure to ambient particulate matter in India. Nature Commun 9(1):617, PMID: 29434294, https://doi.org/10.1038/s41467-018-02986-7.

Dadvand P, Parker J, Bell ML, Bonzini M, Brauer M, Darrow LA, et al. 2013. Maternal exposure to particulate air pollution and term birth weight: a multi-country evaluation of effect and heterogeneity. Environ Health Perspect 121(3):267–373, PMID: 23384584, https://doi.org/10.1289/ehp.1205575.

Desaigues B, Ami D, Bartczak A, Braun-Kohlová M, Chilton S, Czajkowski M, et al. 2011. Economic valuation of air pollution mortality: a 9-country contingent valuation survey of value of a life year (VOLY). Economic Indicators 11(3):902–910, https://doi.org/10.1016/j.ecolind.2010.12.006.

Di Q, Wang Y, Zanobetti A, Wang Y, Koutrakis P, Choirat C, et al. 2017. Air pollution and mortality in the Medicare population. N Engl J Med 376(26):2513–2522, PMID: 28657878, https://doi.org/10.1056/NEJMoa1702747.

Diamanti-Kandarakis E, Bourguignon J-P, Giudice LC, Hauser R, Prins GS, Soto AM, et al. 2009. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr Rev 30(4):293–342, PMID: 19502515, https://doi.org/10.1210/er.2009-0002.

Ebi KL, Hasegawa T, Hayes K, Monaghan A, Paz S, Berry P. 2018. Health risks of warming of 1.5°C, 2°C and higher, above pre-industrial temperatures. Environ Res Lett 13(6):063007, https://doi.org/10.1088/1748-9326/aac4bd.

El Majidi N, Bouchard M, Carrier G. 2013. Systematic analysis of the relationship between standardized prenatal exposure to polychlorinated biphenyls and mental and motor development during follow-up of nine children cohorts. Regul Toxicol Pharmacol 66(1):130–146, PMID: 23524270, https://doi.org/10.1016/j.yrtph.2013.03.002.

Ezzati M, Lopez AD, Rodgers A, Murray CJL. 2004. *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*. Geneva, Switzerland: WHO.

Fatmi Z, Coggon D. 2016. Coronary heart disease and household air pollution from use of solid fuel: a systematic review. Br Medical Bull 118(1):91, PMID: 27151956, https://doi.org/10.1093/bmb/ldw015.

Fewtrell LJ, Prüss-Üstün A, Landrigan P, Ayuso-Mateos JL. 2004. Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure. Environ Res 94(2):120–133, PMID: 14757375, https://doi.org/10.1016/S0013-9351(03)00132-4.

Flegal RA, Smith DR. 1992. Lead levels in preindustrial humans. N Engl J Med 326(19):1293–1294, PMID: 1560812.

Fleischer NL, Merialdi M, van Donkelaar A, Vadillo-Ortega F, Martin RV, Betran AP, et al. 2014. Outdoor air pollution, preterm birth, and low birth weight: analysis of the World Health Organization Global Survey on Maternal and Perinatal Health. Environ Health Perspect 122(4):425–430, PMID: 24508912, https://doi.org/10.1289/ehp.1306837.

Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. 2018. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. Lancet 392(10159):2052–2090, PMID: 30340847, https://doi.org/10.1016/S0140-6736(18)31694-5.

Forouzanfar MH, Afshin A, Alexander LT, Anderson HR, Bhutta ZA, Biryukov S, et al. 2016. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388(10053):1659–1724, PMID: 27733284, https://doi.org/10.1016/S0140-6736(16)31679-8.

Friedman L, Friedman M. 2016. Financial conflicts of interest and study results in environmental and occupational health research. J Occup Environ Med 58(3):238–247, PMID: 26949873, https://doi.org/10.1097/JOM.0000000000000671.

Galán I, Prieto A, Rubio M, Herrero T, Cervigón P, Cantero JL, et al. 2010. Association between airborne pollen and epidemic asthma in Madrid, Spain: a case–control study. Thorax 65(5):398, PMID: 20435860, https://doi.org/10.1136/thx.2009.118992.

Garcia-Saenz A, Sánchez de Miguel A, Espinosa A, Valentin A, Aragonés N, Llorca J, et al. 2018. Evaluating the association between artificial light-at-night exposure and breast and prostate cancer risk in Spain (MCC-Spain Study) Environ Health Perspect 126(4):047011, PMID: 29687979, https://doi.org/10.1289/EHP1837.

GBD MAPS (Global Burden of Disease from Major Air Pollution Sources) Working Group. 2016. *Burden of Disease Attributable to Coal-Burning and Other Air Pollution Sources in China. Special, Report 20*. Boston, MA: Health Effects Institute.

GBD MAPS Working Group. 2018. *Burden of Disease Attributable to Major Air Pollution Sources in India, Special Report 21*. Boston, MA: Health Effects Institute.

GBD Population and Fertility Collaborators. 2017. Population and fertility by age and sex for 195 countries and territories, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1995–2051, PMID: 30496106, https://doi.org/10.1016/S0140-6736(18)32278-5.

Gennaro V, Tomatis L. 2005. Business bias: how epidemiologic studies may underestimate or fail to detect increased risks of cancer and other diseases. Int J Occup Environ Health 11(4):356–359, PMID: 16350469, https://doi.org/10.1179/oeh.2005.11.4.356.

Gordon SB, Bruce NG, Grigg J, Hibberd PL, Kurmi OP, Lam K-B. H, et al. 2014. Respiratory risks from household air pollution in low and middle income countries. Lancet Respir Med 2(10):823–860, PMID: 25193349, https://doi.org/10.1016/S2213-2600(14)70168-7.

Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. 2015. Executive summary to EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocrine Rev 36(6):593–602, PMID: 26414233, https://doi.org/10.1210/er.2015-1093.

Graetz N, Friedman J, Osgood-Zimmerman A, Burstein R, Biehl MH, Shields C, et al. 2018. Mapping local variation in educational attainment across Africa. Nature 555(7694):48, PMID: 29493588, https://doi.org/10.1038/nature25761.

Grandjean P, Bellanger M. 2017. Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation. Environ Health 16(1):123, PMID: 29202828, https://doi.org/10.1186/s12940-017-0340-3.

Grandjean P, Landrigan PJ. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368(9553):2167–2178, PMID: 17174709, https://doi.org/10.1016/S0140-6736(06)69665-7.

Grandjean P, Landrigan PJ. 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol 13(3):330–338, PMID: 24556010, https://doi.org/10.1016/S1474-4422(13)70278-3.

Grosse SD, Matte TD, Schwartz J, Jackson RJ. 2002. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ Health Perspect 110(6):563–569, PMID: 12055046, https://doi.org/10.1289/ehp.02110563.

Guarnieri M, Balmes JR. 2014. Outdoor air pollution and asthma. Lancet 383(9928):1581–1592, PMID: 24792855, https://doi.org/10.1016/S0140-6736(14)60617-6.

Haagsma JA, Maertens de Noordhout C, Polinder S, Vos T, Havelaar AH, Cassini A, et al. 2015. Assessing disability weights based on the responses of 30,660 people from four European countries. Popul Health Metr 13:10, PMID: 26778920, https://doi.org/10.1186/s12963-015-0042-4.

Hauser R, Skakkebaek NE, Hass U, Toppari J, Juul A, Andersson AM, et al. 2015. Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metab 100(4):1267–1277, PMID: 25742517, https://doi.org/10.1210/jc.2014-4325.

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. 2013. Long-term air pollution exposure and cardio-respiratory mortality: a review. Environ Health 12(1):43, PMID: 23714370, https://doi.org/10.1186/1476-069X-12-43.

Hu H, Galea S, Rosella L, Henry D. 2017. Big data and population health: focusing on the health impacts of the social, physical, and economic environment. Epidemiology 28(6):759–762, PMID: 28682850, https://doi.org/10.1097/EDE.0000000000000711.

Hu H, Landrigan PJ, Fuller R, Lim SS, Murray C. 2018. New initiative aims at expanding Global Burden of Disease estimates for pollution and climate. Lancet Planet Health 2(10):e415–e416, PMID: 30318094, https://doi.org/10.1016/S2542-5196(18)30189-X.

Hu H, Rabinowitz M, Smith D. 1998. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: conceptual paradigms. Environ Health Perspect 106(1):1–8, PMID: 9417769, https://doi.org/10.2307/3433626.

Hu H, Shih R, Rothenberg S, Schwartz BS. 2007. The epidemiology of lead toxicity in adults: measuring dose and consideration of other methodologic issues. Environ Health Perspect 115(3):455–462, PMID: 17431499, https://doi.org/10.1289/ehp.9783.

Hu H, Téllez-Rojo MM, Bellinger D, Smith D, Ettinger AS, Lamadrid-Figueroa H, et al. 2006. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development. Environ Health Perspect 114(11):1730–1735, PMID: 17107860, https://doi.org/10.1289/ehp.9067.

Huff J. 2007. Industry influence on occupational and environmental public health. Int J Occup Environ Health 13(1):107–117, PMID: 17427355, https://doi.org/10.1179/107735207800244929.

IARC (International Agency for Research on Cancer) Working Group. 2012. Arsenic and arsenic compounds. Lyon, France: IARC.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2016. Polychlorinated biphenyls and polybrominated biphenyls: IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC.

IHME (Institute for Health Metrics and Evaluation), World Bank Group. 2016. The Cost of Air Pollution: Strengthening the Economic Case for Action. https://openknowledge.worldbank.org/handle/10986/2501 [accessed 15 March 2019].

IHME. 2018. Protocol for the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). Part 3. Institute for Health Metrics and Evaluation: Seattle, Washington. http://www.healthdata.org/sites/default/files/files/Projects/GBD/GBD_Protocol.pdf [accessed 20 May 2019].

IHME. Scientific Council. 2016. http://www.healthdata.org/gbd/about/scientific-council [accessed 1 March 2019].

IHME. Socio-demographic Index (SDI). http://www.healthdata.org/taxonomy/glossary/socio-demographic-index-sdi [accessed 18 May 2019].

James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1789–1858, PMID: 30496104, https://doi.org/10.1016/S0140-6736(18)32279-7.

Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, et al. 2014. The navigation guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect 122(10):1028–1039, PMID: 24968388, https://doi.org/10.1289/ehp.1307893.

Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, et al. 2012. Evidence on the human health effects of low-level methylmercury exposure. Environ Health Perspect 120(6):799–806, PMID: 22275730, https://doi.org/10.1289/ehp.1104494.

Karanasiou A, Moreno N, Moreno T, Viana M, de Leeuw F, Querol X. 2012. Health effects from Sahara dust episodes in Europe: literature review and research gaps. Environ Int 47:107–114, PMID: 22796892, https://doi.org/10.1016/j.envint.2012.06.012.

Khreis H, Kelly C, Tate J, Parslow R, Lucas K, Nieuwenhuijsen M. 2017. Exposure to traffic-related air pollution and risk of development of childhood asthma: a systematic review and meta-analysis. Environ Int 100:1–31, PMID: 27881237, https://doi.org/10.1016/j.envint.2016.11.012.

Kordas K, Canfield RL, López P, Rosado JL, Vargas GG, Cebrián ME, et al. 2006. Deficits in cognitive function and achievement in Mexican first-graders with low blood lead concentrations. Environ Res 100(3):371–386, PMID: 16169549, https://doi.org/10.1016/j.envres.2005.07.007.

Kurokawa J, Ohara T, Morikawa T, Hanayama S, Janssens-Maenhout G, Fukui T, et al. 2013. Emissions of air pollutants and greenhouse gases over Asian regions during 2000–2008: Regional Emission Inventory in Asia (REAS) version 2. Atmos Chem Phys 13(21):11019–11058, https://doi.org/10.5194/acp-13-11019-2013.

Kyu HH, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. 2018. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1859–1922, PMID: 30415748, https://doi.org/10.1016/S0140-6736(18)32335-3.

Lam J, Lanphear BP, Bellinger D, Axelrad DA, McPartland J, Sutton P, et al. 2017. Developmental PBDE exposure and IQ/ADHD in childhood: a systematic review and meta-analysis. Environ Health Perspect 125(8):086001, PMID: 28799918, https://doi.org/10.1289/EHP1632.

Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Baldé AB, et al. 2018a. The Lancet Commission on Pollution and Health. Lancet 391(10119):462–512, PMID: 29056410, https://doi.org/10.1016/S0140-6736(17)32345-0.

Landrigan PJ, Fuller R, Hu H, Caravanos J, Cropper ML, Hanrahan D, et al. 2018b. Pollution and global health–an agenda for prevention. Environ Health Perspect 126(8):084501, PMID: 30118434, https://doi.org/10.1289/EHP3141.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 113(7):894–899, PMID: 16002379, https://doi.org/10.1289/ehp.7688.

Lanphear BP, Rauch S, Auinger P, Allen RW, Hornung RW. 2018. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Pub Health 3(4):e177–e184, PMID: 29544878, https://doi.org/10.1016/S2468-2667(18)30025-2.

Larkin A, Geddes JA, Martin RV, Xiao Q, Liu Y, Marshall JD, et al. 2017. Global land use regression model for nitrogen dioxide air pollution. Environ Sci Technol 51:6957–6964, PMID: 28520422, https://doi.org/10.1021/acs.est.7b01148.

Legler J, Fletcher T, Govarts E, Porta M, Blumberg B, Heindel JJ, et al. 2015. Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metab 100(4):1278–1288, PMID: 25742518, https://doi.org/10.1210/jc.2014-4326.

Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. 2015. The contribution of outdoor air pollution sources to premature mortality on a global scale. Nature 525(7569):367, PMID: 26381985, https://doi.org/10.1038/nature15371.

Lelieveld J, Klingmüller K, Pozzer A, Pöschl U, Fnais M, Daiber A, et al. 2019. Cardiovascular disease burden from ambient air pollution in Europe reassessed using novel hazard ratio functions. Europ Heart J 40(20):1590, PMID: 30860255, https://doi.org/10.1093/eurheartj/ehz135.

Levy RJ. 2015. Carbon monoxide pollution and neurodevelopment: a public health concern. Neurotoxicol Teratol 49:31–40, PMID: 25772154, https://doi.org/10.1016/j.ntt.2015.03.001.

Lim SS, Updike RL, Kaldjian AS, Barber RM, Cowling K, York H, et al. 2018. Measuring human capital: a systematic analysis of 195 countries and territories, 1990–2016. Lancet 392(10154):1217–1234, PMID: 30266414, https://doi.org/10.1016/S0140-6736(18)31941-X.

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. 2012. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859):2224–2260, PMID: 23245609, https://doi.org/10.1016/S0140-6736(12)61766-8.

Lippmann M, Chen LC, Gordon T, Ito K, Thurston GD. 2013. National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components. Research Report (Health Effects Institute) 177:5–13.

Liu G, Dhana K, Furtado JD, Rood J, Zong G, Liang L, et al. 2018. Perfluoroalkyl substances and changes in body weight and resting metabolic rate in response to weight-loss diets: a prospective study. PLOS Med 15(2):e1002502, PMID: 29438414, https://doi.org/10.1371/journal.pmed.1002502.

Liu J, Li L, Wang Y, Yan C, Liu X. 2013. Impact of low blood lead concentrations on IQ and school performance in Chinese children. PLoS One 8(5):e65230, PMID: 23734241, https://doi.org/10.1371/journal.pone.0065230.

Lozano R, Fullman N, Abate D, Abay SM, Abbafati C, Abbasi N, et al. 2018. Measuring progress from 1990 to 2017 and projecting attainment to 2030 of the health-related sustainable development goals for 195 countries and territories: a systematic analysis for the global burden of disease study 2017. Lancet 392(10159):2091–2138, PMID: 30496107, https://doi.org/10.1016/S0140-6736(18)32281-5.

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. 2017. *Industry sponsorship and research outcome*. Cochrane Database of Systematic Reviews. Issue 2. Art. No.: MR000033. https://doi.org/10.1002/14651858.

Magzamen S, Imm P, Amato MS, Havlena JA, Anderson HA, Moore CF, et al. 2013. Moderate lead exposure and elementary school end-of-grade examination performance. Ann Epidemiol 23(11):700–707, PMID: 24095655, https://doi.org/10.1016/j.annepidem.2013.08.007.

Malley CS, Henze DK, Kuylenstierna JCI, Vallack HW, Davila Y, Anenberg SC, et al. 2017. Updated global estimates of respiratory mortality in adults ⩾30 years of age attributable to long-term ozone exposure. Environ Health Perspect 125(8):087021, PMID: 28858826, https://doi.org/10.1289/EHP1390.

McLaine P, Navas-Acien A, Lee R, Simon P, Diener-West M, Agnew J. 2013. Elevated blood lead levels and reading readiness at the start of kindergarten. Pediatrics 131(6):1081–1089, PMID: 23669514, https://doi.org/10.1542/peds.2012-2277.

McMichael AJ, Campbell-Lendrum D, Kovats RS, Edwards S, Wilkinson P, Wilson T, et al. 2004. Global climate change. In: *Comparative Quantification of Health Risks*. World Health Organization. Geneva, Switzerland: WHO.

Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. 2012. GBD 2010: design, definitions, and metrics. Lancet 380(9859):2063–2066, PMID: 23245602, https://doi.org/10.1016/S0140-6736(12)61899-6.

National Academies of Sciences. 2017a. *Using 21st Century Science to Improve Risk-Related Evaluations*. Washington, DC: National Academies Press.

National Academies of Sciences. 2017b. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. Washington, DC: National Academies Press.

Navas-Acien A, Guallar E, Silbergeld EK, Rothenberg SJ. 2007. Lead exposure and cardiovascular disease–a systematic review. Environ Health Perspectives 115(3):472–482, PMID: 17431501, https://doi.org/10.1289/ehp.9785.

Navas-Acien A, Schwartz BS, Rothenberg SJ, Hu H, Silbergeld EK, Guallar E. 2008. Bone lead levels and blood pressure endpoints: a meta-analysis. Epidemiology: 19(3):496–504, PMID: 18414090, https://doi.org/10.1097/EDE.0b013e31816a2400.

Nieuwenhuijsen MJ, Donaire-Gonzalez D, Rivas I, De Castro M, Cirach M, Hoek G, et al. 2015. Variability in and agreement between modeled and personal continuously measured black carbon levels using novel smartphone and sensor technologies. Environ Sci Technol 49:2977–2982, PMID: 25621420, https://doi.org/10.1021/es505362x.

O'Connell SG, Kincl LD, Anderson KA. 2014. Silicone wristbands as personal passive samplers. Environ Sci Technol 48:3327–3335, https://doi.org/10.1021/es405022f.

OECD (Organization for Economic Cooperation and Development). 2008. Chapter 18: Chemicals. In: *OECD Environmental Outlook to 2030*. Paris, France: OECD Publishing.

Orru H, Andersson C, Ebi KL, Langner J, Åström C, Forsberg B. 2013. Impact of climate change on ozone-related mortality and morbidity in Europe. Eur Respir J 41(2):285–294, PMID: 22743679, https://doi.org/10.1183/09031936.00210411.

Patterson C, Ericson J, Manea-Krichten M, Shirahata H. 1991. Natural skeletal levels of lead in Homo sapiens sapiens uncontaminated by technological lead. Sci Total Environ 107:205–236, PMID: 1785050, https://doi.org/10.1016/0048-9697(91)90260-L.

Payne-Sturges DC, Marty MA, Perera F, Miller MD, Swanson M, Ellickson K, et al. 2019. Healthy air, healthy brains: advancing air pollution policy to protect children's health. Am J Public Health 109(4):550–554, PMID: 30789769, https://doi.org/10.2105/AJPH.2018.304902.

Pearce N, Pekkanen J, Beasley R. 1999. How much asthma is really attributable to atopy? Thorax 54(3):268, PMID: 10325905, https://doi.org/10.1136/thx.54.3.268.

Pinault L, Tjepkema M, Crouse DL, Weichenthal S, van Donkelaar A, Martin RV, et al. 2016. Risk estimates of mortality attributed to low concentrations of ambient fine particulate matter in the Canadian Community Health Survey cohort. Environ Health 15(1):18, PMID: 26864652, https://doi.org/10.1186/s12940-016-0111-6.

Pope CA 3rd, Cohen AJ, Burnett RT. 2018. Cardiovascular disease and fine particulate matter: lessons and limitations of an integrated exposure-response

approach. Circ Res 122(12):1645–1647, PMID: 29880499, https://doi.org/10.1161/CIRCRESAHA.118.312956.
Power MC, Adar SD, Yanosky JD, Weuve J. 2016. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: a systematic review of epidemiologic research. Neurotoxicology 56:235–253, PMID: 27328897, https://doi.org/10.1016/j.neuro.2016.06.004.
Prüss-Ustün A, Wolf J, Corvalán C, Neville T, Bos R, Neira M. 2017. Diseases due to unhealthy environments: an updated estimate of the global burden of disease attributable to environmental determinants of health. J Public Health (Oxf) 39(3):464–475, PMID: 27621336, https://doi.org/10.1093/pubmed/fdw085.
Radwan MA, Salama AK. 2006. Market basket survey for some heavy metals in Egyptian fruits and vegetables. Food Chem Toxicol 44(8):1273–1278, PMID: 16600459, https://doi.org/10.1016/j.fct.2006.02.004.
Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711–718, PMID: 24755067, https://doi.org/10.1289/ehp.1307972.
Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. 2018. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392(10159):1736–1788, PMID: 30496103, https://doi.org/10.1016/S0140-6736(18)32203-7.
Rothman KJ, Greenland S, Lash TL. 2008. *Modern Epidemiology*. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins.
Rusch E, Hare H. 2014. *Identifying and Reducing Environmental Health Risks of Chemicals in Our Society–Workshop Summary*. Washington, DC: National Academies Press.
Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, et al. 2015. Disability weights for the Global Burden of Disease 2013 Study. Lancet Glob Health 3(11):e712–e723, PMID: 26475018, https://doi.org/10.1016/S2214-109X(15)00069-8.
Schecter A, Päpke O, Harris TR, Tung K, Musumba A, Olson J, et al. 2006. Polybrominated diphenyl ether (PBDE) levels in an expanded market basket survey of US food and estimated PBDE dietary intake by age and sex. Environ Health Perspect 114(10):1515, https://doi.org/10.1289/ehp.9121.
Schneider JS, Huang FN, Vemuri MC. 2003. Effects of low-level lead exposure on cell survival and neurite length in primary mesencephalic cultures. Neurotoxicol Teratol 25(5):555–559, PMID: 12972068, https://doi.org/10.1016/S0892-0362(03)00018-7.
Sellers S, Ebi KL. 2017. Climate change and health under the shared socioeconomic pathway framework. Int J Environ Res Public Health 15(1):3, PMID: 29267204, https://doi.org/10.3390/ijerph15010003.
Shaddick G, Thomas ML, Amini H, Broday D, Cohen A, Frostad J, et al. 2018a. Data integration for the assessment of population exposure to ambient air pollution for global burden of disease assessment. Environ Sci Technol 52(16):9069–9078, PMID: 29957991, https://doi.org/10.1021/acs.est.8b02864.
Shaddick G, Thomas ML, Green A, Brauer M, Donkelaar A, Burnett R, et al. 2018b. Data integration model for air quality: a hierarchical approach to the global estimation of exposures to ambient air pollution. J R Stat Soc C 67(1):231–253, https://doi.org/10.1111/rssc.12227.
Sheehan MC, Burke TA, Navas-Acien A, Breysse PN, McGready J, Fox MA. 2014. Global methylmercury exposure from seafood consumption and risk of developmental neurotoxicity: a systematic review. Bull World Health Organ 92(4):254–269F, PMID: 24700993, https://doi.org/10.2471/BLT.12.116152.
Smith AH, Lingas EO, Rahman M. 2000. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. Bull World Health Organ 78(9):1093–1103, PMID: 11019458.
Smith DR, Flegal AR. 1992. The public health implications of humans' natural levels of lead. Am J Pub Health 82(11):1565–1566, PMID: 1332521, https://doi.org/10.2105/AJPH.82.11.1565.
Smith JN. 2015. *Epic Measures: One Doctor, Seven Billion Patients*. New York, NY: Harper Wave.
Smith KR, McCracken JP, Weber MW, Hubbard A, Jenny A, Thompson LM, et al. 2011. Effect of reduction in household air pollution on childhood pneumonia in Guatemala (RESPIRE): a randomised controlled trial. Lancet 378(9804):1717–1726, PMID: 22078686, https://doi.org/10.1016/S0140-6736(11)60921-5.
Smith KR, Woodward A, Campbell-Lendrum D, Chadee DD, Honda Y, Liu Q, et al. 2014. Human health: impacts, adaptation, and co-benefits. In: *Climate Change 2014: Impacts, Adaptation, and Vulnerability: Part A: Global and Sectoral Aspects, Contribution of Working Group II to the Fifth Assessment Report of The Intergovernmental Panel of Climate Change*. Field CB, Barros VR, Dokken DJ, Mach KJ, Mastrandrea MD, Bilir TE, et al., eds. Cambridge and New York: Cambridge University Press, 709–754.
Stanaway JD, Afshin A, Gakidou E, Lim SS, Abate D, Abate KH, et al. 2018. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392:1923–1994, PMID: 30496105, https://doi.org/10.1016/S0140-6736(18)32225-6.
Stanek LW, Sacks JD, Dutton SJ, Dubois JJ. 2011. Attributing health effects to apportioned components and sources of particulate matter: an evaluation of collective results. Atmospheric Environment 45(32):5655–5663, https://doi.org/10.1016/j.atmosenv.2011.07.023.
Taylor M. 2003. Purchasing power parity. Rev Int Econ 11(3):436–452, https://doi.org/10.1111/1467-9396.00394.
Thurston GD, Burnett RT, Turner MC, Shi Y, Krewski D, Lall R, et al. 2016. Ischemic heart disease mortality and long-term exposure to source-related components of U.S. fine particle air pollution. Environ Health Perspect 124(6):785–794, PMID: 26629599, https://doi.org/10.1289/ehp.1509777.
Tolins M, Ruchirawat M, Landrigan P. 2014. The developmental neurotoxicity of arsenic: cognitive and behavioral consequences of early life exposure. Ann Glob Health 80(4):303–314, PMID: 25459332, https://doi.org/10.1016/j.aogh.2014.09.005.
Trasande L, Landrigan PJ, Schechter C. 2005. Public health and economic consequences of methyl mercury toxicity to the developing brain. Environ Health Perspect 113(5):590–596, PMID: 15866768, https://doi.org/10.1289/ehp.7743.
Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, et al. 2016. Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis. Andrology 4(4):565–572, PMID: 27003928, https://doi.org/10.1111/andr.12178.
Tsoi M-F, Cheung C-L, Cheung TT, Cheung B. 2016. Continual decrease in blood lead level in Americans: United States National Health Nutrition and Examination Survey 1999–2014. Am J Med 129(11):1213–1218, PMID: 27341956, https://doi.org/10.1016/j.amjmed.2016.05.042.
Turner MC, Cohen A, Burnett RT, Jerrett M, Diver WR, Gapstur SM, et al. 2017. Interactions between cigarette smoking and ambient $PM_{2.5}$ for cardiovascular mortality. Environ Res 154:304–310, PMID: 28142053, https://doi.org/10.1016/j.envres.2017.01.024.
Turner MC, Cohen A, Jerrett M, Gapstur SM, Diver WR, Pope CA 3rd, et al. 2014. Interactions between cigarette smoking and fine particulate matter in the Risk of Lung Cancer Mortality in Cancer Prevention Study II. Am J Epidemiol 180(12):1145–1149, PMID: 25395026, https://doi.org/10.1093/aje/kwu275.
Turner MC, Jerrett M, Pope CA 3rd, Krewski D, Gapstur SM, Diver WR, et al. 2016. Long-term ozone exposure and mortality in a large prospective study. Am J Respir Crit Care Med 193(10):1134–1142, PMID: 26680605, https://doi.org/10.1164/rccm.201508-1633OC.
U.S. EPA (U.S. Environmental Protection Agency). 2018. Integrated Science Assessment (ISA) for Particulate Matter (external review draft).
Van Donkelaar A, Martin RV, Brauer M, Hsu NC, Kahn RA, Levy RC, et al. 2016. Global estimates of fine particulate matter using a combined geophysical-statistical method with information from satellites, models, and monitors. Environ Science Technol 50(7):3762–3772, PMID: 26953851, https://doi.org/10.1021/acs.est.5b05833.
Vandenberg LN, Ågerstrand M, Beronius A, Beausoleil C, Bergman A, Bero LA, et al. 2016. A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals. Environ Health 15(1):74, PMID: 27412149, https://doi.org/10.1186/s12940-016-0156-6.
Villanueva CM, Kogevinas M, Cordier S, Templeton MR, Vermeulen R, Nuckols JR, et al. 2017. Assessing exposure and health consequences of chemicals in drinking water: current state of knowledge and research needs. Environ Health Perspect 122(3):213–221, PMID: 24380896, https://doi.org/10.1289/ehp.1206229.
Wasserman GA, Factor-Litvak P, Liu X, Todd AC, Kline JK, Slavkovich V, et al. 2003. The relationship between blood lead, bone lead and child intelligence. Child Neuropsychol 9(1):22–34, PMID: 12815520, https://doi.org/10.1076/chin.9.1.22.14497.
Weisskopf MG, Jain N, Nie H, Sparrow D, Vokonas P, Schwartz J, et al. 2009. A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. Circulation 120(12):1056–1064, PMID: 19738141, https://doi.org/10.1161/CIRCULATIONAHA.108.827121.
WHO (World Health Organization). 2013. WHO Methods and Data Sources for Global Burden of Disease Estimates 2000–2011. Geneva, Switzerland: World Health Organization.
WHO Regional Office for Europe. 2013. Review of Evidence on Health Aspects of Air Pollution – REVIHAAP Project: Technical Report. Copenhagen, Denmark: WHO/Europe, World Health Organization.
WHO. 2019. Ten Threads to Global Health in 2019. https://www.who.int/emergencies/ten-threats-to-global-health-in-2019 [accessed 15 May 2019].
Williams P, Raab A, Feldmann J, Meharg A. 2007. Market basket survey shows elevated levels of As in South Central U.S. processed rice compared to California: consequences for human dietary exposure. Environ Sci Technol 41:2178–2183, https://doi.org/10.1021/es061489k.
Woodruff TJ, Sutton P. 2011. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Aff (Millwood) 30(5):931–937, PMID: 21555477, https://doi.org/10.1377/hlthaff.2010.1219.

Woodruff TJ, Sutton P. 2014. The navigation guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect 122(10):1007–1014, PMID: 24968373, https://doi.org/10.1289/ehp.1307175.

Woodruff TJ, Zeise L, Axelrad DA, Guyton KZ, Janssen S, Miller M, et al. 2008. Meeting report: moving upstream-evaluating adverse upstream end points for improved risk assessment and decision-making. Environ Health Perspect 116(11):1568–1575, PMID: 19057713, https://doi.org/10.1289/ehp.11516.

World Cancer Research Fund/American Institute for Cancer Research. 2018. Continuous update project expert report. In: *Judging the Evidence*. https://www.wcrf.org/sites/default/files/judging-the-evidence.pdf [accessed 20 October 2018].

Yan C-H. 2018. Blood Lead Levels in Children Aged 0 to 6 years in China: A National Survey. In: Proceedings of the International Society of Exposure Science - International Society for Environmental Epidemiology Joint Annual Meeting, 2018 Ottawa, Canada, 2018.

Yin P, Brauer M, Cohen A, Burnett RT, Liu J, Liu Y, et al. 2017. Long-term fine particulate matter exposure and nonaccidental and cause-specific mortality in a large national cohort of Chinese men. Environ Health Perspect 125(11):117002, PMID: 29116930, https://doi.org/10.1289/EHP1673.

Ysart G, Miller P, Croasdale M, Crews H, Robb P, Baxter M, et al. 2000. 1997 UK total diet study dietary exposures to aluminium, arsenic, cadmium, chromium, copper, lead, mercury, nickel, selenium, tin and zinc. Food Addit Contam 17(9):775–786, PMID: 11091791, https://doi.org/10.1080/026520300415327.

Yu K, Qiu G, Chan KH, Lam KH, Kurmi OP, Bennett DA, et al. 2018. Association of solid fuel use with risk of cardiovascular and all-cause mortality in rural China. JAMA 319(13):1351–1361, PMID: 29614179, https://doi.org/10.1001/jama.2018.2151.

Zanobetti A, Franklin M, Koutrakis P, Schwartz J. 2009. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environ Health 8:58, PMID: 20025755, https://doi.org/10.1186/1476-069X-8-58.

Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, et al. 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. Environ Health Perspect 108(5):419–426, PMID: 10811568, https://doi.org/10.2307/3454382.

Zhang N, Baker HW, Tufts M, Raymond RE, Salihu H, Elliott MR. 2013. Early childhood lead exposure and academic achievement: evidence from Detroit public schools, 2008–2010. Am J Public Health 103(3):e72–e77, PMID: 23327265, https://doi.org/10.2105/AJPH.2012.301164.

Zhang Q, Jiang X, Tong D, Davis SJ, Zhao H, Geng G, et al. 2017. Transboundary health impacts of transported global air pollution and international trade. Nature 543(7647):705, PMID: 28358094, https://doi.org/10.1038/nature21712.

Zhao B, Zheng H, Wang S, Smith KR, Lu X, Aunan K, et al. 2018. Change in household fuels dominates the decrease in $PM_{2.5}$ exposure and premature mortality in China in 2005–2015. Proc Natl Acad Sci USA 115(49):12401–12406, PMID: 30455309, https://doi.org/10.1073/pnas.1812955115.

Zhu C, Kobayashi K, Loladze I, Zhu J, Jiang Q, Xu X, et al. 2018. Carbon dioxide (CO_2) levels this century will alter the protein, micronutrients, and vitamin content of rice grains with potential health consequences for the poorest rice-dependent countries. Sci Adv 4(5):eaaq1012, PMID: 29806023, https://doi.org/10.1126/sciadv.aaq1012.

Ziska L, Knowlton K, Rogers C, Dalan D, Tierney N, Elder MA, et al. 2011. Recent warming by latitude associated with increased length of ragweed pollen season in central North America. Proc Nat Acad Sci USA 108(10):4248, PMID: 21368130, https://doi.org/10.1073/pnas.1014107108.

Zoeller RT, Bergman Å, Becher G, Bjerregaard P, Bornman R, Brandt I, et al. 2014. A path forward in the debate over health impacts of endocrine disrupting chemicals. Environ Health 13:118, PMID: 25533907, https://doi.org/10.1186/1476-069X-13-118.

Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. Endocrinology 153(9):4097–4110, PMID: 22733974, https://doi.org/10.1210/en.2012-1422.